New Medications.

PART II.

By Prof. Dujardin-Beaumetz.

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NEW MEDICATIONS.

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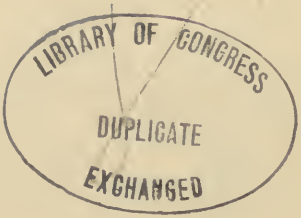

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NEW MEDICATIONS.

PART II.

CHAPTER VIII.

ON ANTISEPTIC PULMONARY MEDICATION.

GENTLEMEN: One may affirm without fear of being accused of exaggeration, that antiseptic pulmonary medication, such as we may ideally imagine it to be, is destined to have a high place in the therapeutics of the future. In fact, in all that concerns the contagion of diseases, the air is the most important factor, and whoever shall succeed in depriving the atmosphere of its germs, will render the greatest possible service to medicine and hygiene.

Thanks to the brilliant discoveries of Pasteur, and to Miquel's patient investigations, we know to-day by scientific means, not only the number of the micro-organisms which flit about in the air, but also the divers varieties of these microbes, which belong especially to the genera micrococcus, bacillus, and bacterium, but more particularly to the first of these genera.

Microbiologists have even gone further; they have commenced the study of these different schizo-

phytes from a botanical point of view, as well as from a physiological; and there is one fact which we have learned from these studies, namely, that when the bacteria thus collected from the air have been cultivated in suitable media and inoculated in animals they have given rise to nothing but negative results, and it has not yet been possible to reproduce in animals contagious diseases by the introduction of these micro-organisms. But, as Miquel has justly remarked, these results should be accepted with the greatest reservation, and one may well ask if the procedures put in usage for the collection and cultivation of the schizophytes may not be sufficient to destroy their virulent properties.

As you might have foreseen, the greater part of these micro-organisms—that is to say, eighty per cent. —are aërobiotic—*i. e.*, they have need of oxygen to live and develop.

As for their number, I showed you in one of my late lectures that this varies according to the localities where they are collected, and that the purity of the air is in inverse proportion to the microbes it contains. While in high altitudes you find but very few microbes to each cubic metre of air, it is by the thousands that you meet with them in our hospital wards; and when you reflect that a man breathes through his lungs in twenty-four hours ten cubic metres of air, you can form an estimate of the prodigious number of micro-organisms which penetrate by this channel, which

forms the most easy and rapid mode of entrance into the organism of infectious or medicinal principles. In fact, substances which penetrate by the lungs, are carried almost directly to the left ventricle, and thence are distributed through the entire organism, and this explains the interest which Claude Bernard took in the method of tracheal medicinal injections in cases of urgency.

I am well aware that, by a lucky anatomical conformation, man breathes only exceptionally by the mouth, and that the air penetrates chiefly by the nasal fossæ, which, by their anfractuosities, act the part of the filtering apparatus employed by Pasteur to purify the air, but this infiltration is often very incomplete, since it is by the pulmonary passages that the contagious and infectious diseases are chiefly transmitted.

I cannot here, in this purely medical lecture, discuss in its entirety the subject of antiseptic pulmonary medication, which, by its developments, constitutes one of the grandest chapters of modern hygiene.

I shall only refer in this connection to the divers experiments in which you took part on the occasion of the recent cholera epidemic, when Dr. Roux and myself, under the direction of M. Pasteur, showed that of all the antiseptic gases, the most effective is sulphurous acid, and this chiefly by reason of its power of penetration. We proved that in the proportion of twenty grammes to each cubic metre of space, sulphur in undergoing combustion destroys the micro-

organisms contained in a liquid, and that in the proportion of forty grammes to each cubic metre it destroys the same micro-organisms in a state of desiccation. But in such media man cannot live, and what we want especially to find, is some safe disinfectant, whether liquid or gaseous, which will destroy the schizophytes, while permitting man to sojourn in the medium where this disinfection is practiced.

I know that researches in this direction are being earnestly pursued, and that hope has been entertained that we may find in ozone one of these parasiticide agents, but thus far experiments have not given results confirmed with all the scientific rigor which such researches demand. Others, going back to a notion already put in practice in the Middle Ages, have thought that the introduction of these micro-organisms into the economy might be avoided by the application of protective masks or respirators, such as are used in work-shops and factories where the air becomes impregnated with noxious dust; the breathing air being filtered through layers of cotton. I will not dwell longer on this point, desiring merely to hint at this side of antiseptic pulmonary medication. But there is another aspect of the question on which I desire to dwell longer, it is that which concerns the destruction of certain micro-organisms which are the efficient cause of pulmonary affections, and I wish in particular to say something about the action of antiseptic substances on the microbe of tuberculosis.

When at the end of 1882 Koch, in his remarkable communication, demonstrated the microbiotic nature of phthisis, he by this discovery revolutionized the history of tuberculosis, and gave a striking experimental confirmation of the theory advocated many years before by my learned colleague and friend Dr. Villemin.

When Villemin in 1865, in his brilliant work on tuberculosis, announced that this disease was virulent, contagious, and inocuable, he raised in the medical world a real tempest, which was not allayed at the time of Koch's researches, and many of the most eminent physicians disputed several of the terms of Villemin's definition. To-day all disputation has ceased before experimentation, and everybody is agreed that the bacillus tuberculosis is the real contagious agent of this disease.

But the application of Pasteur's views was destined not to be limited to tuberculosis; these views were soon to modify and revolutionize a disease which has been considered as a type of inflammatory diseases. On the 19th of November, 1883, Friedlander, completing the first researches which he had made in 1882, showed by decisive experiments that there exists a schizophyte proper to pneumonia, and a few days later, namely, November 30th, Talamon, at the Anatomical Society, made known the result of his researches, and showed that if he did not absolutely agree with Friedlander respecting the form of the

bacillus observed, he none the less considered it as the causal agent in pneumonia.

These experimentors thus gave justification to the tentatives made in 1878 by Klebs, who, under the name of *monas pulmonale*, had described a microbe peculiar to pneumonia.

This discovery of a micro-organism as cause of certain pulmonary affections, ought to be utilized by therapeutics; and just as in basing myself on new experimental researches I endeavored to establish an antiseptic intestinal medication, so also I would venture to suggest the first principles of an anti-microbic pulmonary medication.

Let us see first what data experimentation can furnish us, and here I shall take as my basis the labors recently undertaken in France, and, in particular, the able researches of Hippolyte Martin, who has performed experiments of the greatest interest on tubercle and inoculation by tubercle.

Hippolyte Martin first established the fact that inoculation constitutes the best means of recognizing the real nature of tubercle. When, in fact, you inoculate in animals—guinea-pigs or hares—foreign bodies, or septic matters, you determine in these animals granulations more or less generalized in all the viscera, and which macroscopically and microscopically are identical with tubercles. But that which enables us to distinguish pseudo-tubercles from true tubercles, is that the former have no power to produce tuberculo-

sis in other animals, while, on the contrary, true tubercle indefinitely reproduces the same disease in animals in which it is inoculated, so that even before the discovery of Koch's bacillus (as early as 1881), Hippolyte Martin had been able experimentally to demonstrate the proposition: *Tubercle alone engenders tubercle.*

From these experiments this capital fact is put in clear light: That when you would judge of the real value of antiseptic substances in the destruction of the bacillus of tuberculosis, it is not sufficient to practice one inoculation alone, which may cause the production of pseudo-tuberculous granulations, but the inoculations should be in series—*i. e.*, the product of one inoculation being inoculated in another animal, and so on; and all experimentors who have not taken care to avoid this source of error, must expect to see their results called in question.

Repeating the experiments of Arloing, of Cornevin, and of Thomas, who had made trials of the different antiseptic agents to antagonize the anthracoid bacteria, Hippolyte Martin, in his turn, experimented with these antiseptics against the bacillus tuberculosis. This was his procedure: He crushed and pressed portions of viscera studded with tubercles,

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* Hippolyte Martin on Transformation of True or Infectious Tubercle into an Inert Foreign Body under the influence of High Temperature and Various Reagents. Arch dé Phys., 1881, p. 93; Revue de Méd., 1882, t. ii, p. 905, and 1883, t. iii, p. 209.

and the juice which he squeezed out was put in contact with the fresh amniotic liquor of a sheep, and to the whole was added a given quantity of the medicament to be experimented with; in this way trials were made with salicylic acid, bromine, carbolic acid, creasote, quinine, and corrosive sublimate. These mixtures were injected into the peritoneum of guinea-pigs, and on the death of the animals the inoculations were continued in order to ascertain the real value of the granulations which were found at the autopsy.

In the case of salicylic acid, solutions of five-per-cent. were powerless to destroy tubercle. Bromine in solution, 1 per 10,000, and 1 per 1,000, proved to be inefficacious; at 1:500 the action was more marked, but in this strength the solutions are caustic. In the case of phenic acid, solutions of 1:1000 had no effect, and even those of 3:100 or 6:100 had a doubtful action, although caustic effects were manifest. Creasote, so much vaunted in tuberculous affections, failed to destroy the bacillus of tuberculosis, even in the proportion of 1 per 1,000; and it was the same with quinine. In fine, corrosive sublimate, which has justly been considered as one of the most powerful antiseptics, proved itself without action upon the micro-organism of tuberculosis even in the proportion of 1 per 1,000.

What do all these experiments go to show? This, surely, that the tuberculous element offers an extraordinary resistance to all antiseptic agents, and that,

in order to destroy it, you must at the same time destroy the living tissues which are its habitat.* In these experiments we must, in fact, carefully distinguish the antiseptic from the caustic action. When you destroy by a physical or chemical agent the elements of a tissue, you thereby abolish its virulent properties; this is, for example, what happens by heat. Hippolyte Martin, in fact, obtained destruction of the tubercle bacillus by heat, and true tubercle was transformed into an inert body when the temperature of 84°C. was exceeded, and this result was the more certainly attained by a temperature of 100° C. and above.

In a manuscript note, which Hippolyte Martin has kindly put into my hands, he signalizes the favorable effects of hydrofluoric acid, which in the proportion of 1 per 3,000 and, perhaps, of 1 per 4,000, appears to be destructive to the parasite of tubercle. But we must not, at the same time, forget the extreme causticity of this acid, which acts much more as a destroyer of tissue than as a veritable antiseptic.

However, all the experimentors have not arrived at the same conclusions as Hippolyte Martin. Thus it is that Vallin, in the interesting communication

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* Koch, in his paper on "Bacteriological Research," read at the Tenth International Congress, held in Berlin, August 4–10th, 1890, announced that he had found a means of arresting tuberculosis. It is to be hoped that some discovery of importance has been made in this field of inquiry. Dr. Koch has not yet made known the means employed. TRANSLATOR.

made this year to the Academy of Medicine, has shown that burning sulphur, in the proportion of one ounce to the cubic metre, destroys the virulent properties of tubercle juice. Corrosive sublimate, in the proportion of 1 per 1,000, has the same action, but in that of 1 per 2,000 it is inefficacious, while nitrosyle, in the proportion of 66 centigrammes per cubic metre, also causes sterilization of tubercle juice. Vallin's procedure was a little different from that of Hippolyte Martin; he made use of strips of filter paper soaked in distilled water; between these strips tuberculous products were crushed, then the paper was dried in the open air, and submitted to the action of divers disinfecting agents; they were finally soaked again in distilled water, and the liquid obtained by expression was injected into the peritoneum of guinea-pigs.

A physician of Allevard, Dr. Niepce, has lately affirmed that sulphuretted hydrogen destroys the bacillus of tuberculosis in the sputa of phthisical patients, and that the sputa thus acted upon become powerless to induce tuberculosis in animals.

A graduate of the school of Montpellier, Dr. Pilate, has repeated, with the aid of Drs. Cavalier and Mairet, the experiments of Niepce, and he affirms that of all the agents with which he has experimented, such as mercuric iodide, corrosive sublimate, helenin, thymol, iodine, carbolic acid, boric acid, the most active is sulphuretted hydrogen. Dr. Sormani and Brugnatelli claim to have obtained an antibacillary

action with a certain number of liquids, and even in feeble doses. On the other hand, the experiments made in 1883 by Coze and Simon are absolutely confirmative of those of Hippolyte Martin. These experimentors have divided their researches into three groups. In the first series they mix forty centigrammes of phthisical sputa, in which they had previously noted the presence of bacilli, with different antiseptic substances; then, after forty-eight hours' contact, they injected these mixtures in guinea-pigs in the region of the groin.

In a second series of experiments they injected only tuberculous matter; then they practised immediately afterward, and for several days in succession, antiseptic injections in the region of the first tuberculous inoculation.

Finally in the third series of experiments, they endeavored to see if they could arrest the development of the disease in animals already the subjects of tuberculous evolution.

They thus, in their three series of experiments, made trials of bichloride of mercury, eucalyptol, sulphuretted hydrogen, creasote, helenin, thymol, etc. The last two series of researches gave nothing but negative results, and as for the first, creasote alone seemed to them to retard the local development of tuberculosis.

What conclusion shall we draw from these experimental researches. Must we admit that in man

the bacillus tuberculosis resists all our therapeutic measures? Such a conclusion, gentlemen, would be altogether too premature. These experiments show us that in animals such as the guinea-pig and hare, which present a singularly favorable soil for the development of tuberculosis, our medicinal agents prove themselves impotent to destroy the bacillus. But this is not the case with animal species which offer a better resistance to the bacillus—the dog, for instance—and here we see the bacillary inoculations often fail. It is the same with man, and before the discovery of Koch (as well as since) we were in possession of unimpeachable observations showing the cure of bacillary phthisis. So, while recognizing the useful indications furnished by experimental researches, we must, in order to appreciate their just value, turn to clinical observation.

The discovery of the bacillus, and the experiments which we have just mentioned, indicate to us the therapeutic paths which we are henceforth to pursue, and which comprehend two principal lines of investigation:—The one, by which we are to endeavor through medicinal means to oppose the multiplication of bacilli, and the other, by which we seek through hygienic means so to modify the culture medium, that it shall be unfit for the habitat of the bacilli.

Prof. Germain Sée, in his work on *Bacillary Phthisis*, has insisted at great length on the new de-

parture which ought to be taken by the therapeutics of tuberculosis since Koch's discovery, and what conditions shall be fulfilled by the antivirulent agent, which he calls *necrophytic*.

In the first group of agents, we have chiefly medicinal inhalations, and medicaments which are eliminated by the lungs.

Among the medicinal inhalations, it is substances such as iodine, iodoform, eucalyptol, corrosive sublimate, phenic acid, etc.—in a word, the least irritant antiseptic agents – which should be recommended; and our late venerated master, Piorry, seemed to have had prevision of its parasiticide power, when, with such persistence, he insisted on the utility of iodine inhalations in tuberculosis. I believe, also, that iodoform, so much vaunted these late years, may be utilized in these inhalations, being not only a very active antiseptic agent, but also a powerful sedative.

You know how these inhalations are practised. They consist in aspirating a current of air through medicinal solutions, and breathing the air thus medicated. A wash-bottle with two tubes communicating with the exterior (one tube dips beneath the liquid), answers the purpose. You can, if you prefer, use the inhaler of Le Fort, or Lille, in which the air penetrates to the liquid through holes in the sides. Le Fort puts into his bottle the following mixture: Camphor, 8 parts; tar, 4 parts; tincture of iodine, 4 parts; Hoffman's anodyne, 1 part. You may also employ

some of the more complicated inhalers, in which the air is not aspirated by the patient, but projected upon him by a ventilator operating by clock-work, as in Haro's apparatus.* Haro uses iodoform principally, in the pulverization of which it is necessary that the temperature of the mixture should be kept raised. You have seen me use in one of our wards an ingenious vaporizer devised by M. de Linières. This vaporizer, which is put in operation by a rotary movement, projects into the ward vapor of water charged with iodoform; hut it will take us many months to estimate at their just value the effects of these vaporizations of iodoform upon our tuberculous patients. And now, while on this subject of antiseptic inhalations, I ought to speak to you of the experiments being performed at the present time by my pupil, Dr. Chevy, with hydrofluoric acid, experiments which have been made the subject of his inaugural thesis.

Struck by the results indicated by Hippolyte Martin, demonstrating the remarkable antibacillary action of hydrofluoric acid in tuberculosis, it occurred to me to employ this acid in inhalations; Dr. Bergeron had pointed out the extraordinary effects which he had obtained from the vapors of this acid in the treatment of diphtheria, while Chevy and myself were

* Haro: On a New Kind of Inhalations Practised at Amelie les Bains; Bull. de Thérap., t. cvi. p. 408.

Le Fort: On a New Inhaler, and its Action in Pulmonary Affections; Bull. de Thérap., t. ci. p. 343.

showing that animals might live without inconvenience in an atmosphere containing 1 part of hydrofluoric acid to 1155 parts of air.

Moreover, a careful investigation made in the great establishments where hydrofluoric acid is used for etching on glass, enabled us to determine, not only that an atmosphere thus charged with hydrofluoric vapors is not injurious to the workmen, but that, on the contrary, individuals suffering from chest affections had experienced favorable effects therefrom; on this point the overseers of the works are unanimous.

We have since then been experimenting by placing our patients in a special ward, of a capacity of about twenty-two cubic metres, in which apartment we vaporized one grain of pure hydrofluoric acid (which would give the proportion of about 1 part to 25,000); the liberation of the hydrofluoric acid is obtained by placing the liquid in a small leaden cup heated in a sand-bath. Our tuberculous patients remain an hour in this atmosphere. I can say nothing as yet of the results which this experimentation may give; before formulating any positive conclusions, these trials must be continued for months, and even years.

What I can, however, affirm, is, that in the immense majority of cases these inhalations of hydrofluoric acid have not been at all inconvenient to our patients. Some of them have experienced a little irritation in the throat, due to the local action of the acid,

but the majority have derived a certain benefit in the way of diminution of the cough and expectoration. I am inclined to think that these inhalations, in their application to the treatment of tuberculosis, constitute a remedy of much promise.

But permit me, since I am now on the subject of hydrofluoric acid, to say, that of all the antiseptics known, this is, perhaps, the most powerful, and in the experiments which Chevy and I undertook, it required but infinitesimal quantities to arrest fermentation. I now come back again to my subject, and mention among the means to employ in the treatment of phthisis, antiseptic sprays.

In my opinion these latter are very much inferior to the inhalations, for it is only exceptionally that these pulverizations penetrate to the interior of the lungs. Dr. Miquel, however, claims to have obtained good results in tuberculosis from pulverizations of the following mixture: Biniodide of mercury, 1 part; laudanum, 20 parts; distilled water, 2,000 parts.

In order to obtain a more immediate action, it has been advised to inject the antivirulent solutions directly into the pulmonary parenchyma. The practice has been attempted in Germany by Heller, who has thus made, in three patients affected with phthisis, intra-parenchymatous injections of corrosive sublimate in solution.

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* Chevy: Thèse de Paris, 1885, and Bull. de Thérap., April 15, 1885.

In France, Prof. Lepine and his pupil, Truc, have repeated these experiments. They employ alcohol at 90° containing a variable proportion of cresote, 2 to 4 per cent.; they use for these injections the syringe of Pravaz with the No. 1 needle of Dieulafoy's aspirator, and have already performed twenty-five injections on fifteen patients, introducing each time into the parenchyma of the lungs a quantity of the cresote solution varying from a few drops to fifteen or twenty cubic centimetres.

The results thus far have been uncertain, and in patients affected with advanced lesions they have observed hardly any symptoms of amelioration. Therefore, Lepine and Truc speak very reservedly respecting the definite curative value of these parenchymatous injections, and, for my part, I think that these injections are liable to be more dangerous than useful.

Internally, it is still to such medicaments as creosote, the turpentines, the sulphur preparations, that you will resort; these may render service by their elimination by the pulmonary passages. But whatever parasiticide action these agents may be supposed to possess, they must still yield the palm to the modifiers of nutrition, which render the organic soil unfit for the microbes.

Until by a more exact acquaintance with the bacillus and the conditions of its culture and development we shall be able, as in the case of anthrax, to pre-

pare an attenuated virus which, by its inoculation in man, shall preserve him from being the prey to these bacilli, we must direct all our efforts to create in individuals predisposed to tuberculosis a soil unfavorable for the culture of the bacillus. To obtain this result we must utilize two factors; air and alimentation.

Although we have not very precise data respecting the action of the air under different degrees of pressure on the micro-organism of tuberculosis, and researches are needed before we can come to any definite conclusion on this point, we have very good evidence that high altitudes are unfavorable to these bacilli, and even destroy them. The law established by Jourdanet, that at certain altitudes phthisis does not exist, finds a certain confirmation in this fact, that the higher you go, the fewer the microbes you find in the air.

As for alimentation, the method first brought into vogue by Debove has proved to be of the highest utility, and it is to-day generally admitted that, in certain cases where the integrity of the digestive tube is complete, one may, by super-alimentation, obtain amelioration and even cure in pulmonary consumption. The important communication of Broca and Wins* has given us many conclusive observations to this effect, and my pupil, Dr. Pennel, published in

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* Broca and Wins: Bull. de Thér., 1883, t. cv., p. 289.

1882 a series of cases where the beneficial action of forced feeding was most manifest,* and I am astonished that the homœopathic physicians who often give such scrupulously nice attention to the details of their hygienic treatment, have rejected, as Jousset has done, the employment of super-alimentation, by powders of meat, for a vegetarian regimen.

I cannot here enter into the details of this super-alimentation; you know that, by reason of recent improvements in the manufacture of meat powder, we can now give the latter in chocolate and in syrups, a consequence of which is that we do not now employ gavage in pulmonary complaints, reserving it exclusively for patients affected with dilatation of the stomach or persistent vomiting of food. Here, too, I have abandoned the stomach tube which I formerly used, and which goes by the name of "*gaveuse*," for the tube of Debove, which, owing to its resistence and small volume, is introduced without the least difficulty.

What I can affirm, is that in tuberculous patients that have profound and obstinate anorexia, or that vomit their food under the influence of the least effort of coughing, gavage will sometimes give you exceptionally good results. Under its influence the appetite returns, the strength improves, and what is a singular fact, and one not well explained, is that while all food

* Pennel: Alimentation in Phthisis, Bull. de Thér., t. cii., p. 85.

introduced by the mouth is vomited, the alimentary mixtures introduced directly into the stomach by the syphon are well supported. I assign then a preponderant rôle to super-alimentation in the antiseptic treatment of tuberculosis, and this, because it constitutes, in my opinion, our most powerful means of modifying the culture soil.

As you see now, if Koch's discovery has not already revolutionized the therapeutics of pulmonary phthisis, it has nevertheless enabled us to give a scientific explanation of the modus operandi of the greater part of the medicinal agents which we use, and for this very reason it constitutes a step in progress, both from a therapeutic and a prophylactic point of view. This great fact of the contagiousness of tuberculosis is to-day admitted without dispute, and we see on all sides hygienists as well as physicians endeavor to establish on a scientific basis the hygiene of the tuberculous. When you reflect that at this very time (December, 1885) scarcely three years have elapsed since the discovery of the microbe of tuberculosis, and consider the large number of scientific researches and the already voluminous literature to which it has given rise, you cannot fail to entertain the hope that the day will come when, better enlightened as to the life history and mode of development of the bacillus, we shall be able to destroy it in the living organism, or at least attenuate its effects.

Translator's Note.—In a "conference" on "New Anti-

septic Methods of Treating Pulmonary Diseases" (*Therapeutic Gazette*, Nov., 1887), Dujardin-Beaumetz speaks of subcutaneous injections of phenic acid in phthisis, gaseous rectal injections of sulphuretted hydrogen, liquid vaselin, and inhalations of sulphurous acid.

The phenic acid injections may be made directly under the skin, or the needle may be plunged deeply into the soft parts, and even to the seat of the lesion when the injection is made in the region of the thorax. A two-per-cent. solution is used; of this a hypodermic syringeful is injected, but the syringe must be larger than the ordinary kind; it should hold at least a fluid drachm. The phenic acid should be pure, and the solution should be made in glycerin rather than in alcohol.

The best place for the injection is the anterior part of the chest, under the clavicle. The number of punctures should vary from two each week to two each day, according to the gravity and course of the disease. Under no circumstances should they be too often repeated, on account of the dangers of carbolic acid poisoning. In spite of some disasters, the injections of phenic acid have given quite favorable results in a certain number of cases. Almost always the appetite is improved, and the cough, expectoration and night sweats diminished.

The gaseous rectal injections, first proposed by Bergeron of Lyons, have at this date gone completely out of vogue.

The liquid vaselin is now largely employed in the therapeutics of pulmonary complaints under the name of "liquid albolen." A peculiar kind of hand atomizer, now sold by all the principal pharmacists, is much used for the purpose. Liquid vaselin is also a handy vehicle for hypodermic injections; it dissolves eucalyptus, iodine, chloroform, bromine sulphide of carbon, terpinol, and a variety of other substances. Dujardin Beaumetz prefers the combination of medicinal liquid vaselin with eucalyptus in the forms of tuberculosis

with abundant bronchial secretion; it rapidly diminishes the cough, expectoration, and oppression. His formula is as follows:

℞ Pure eucalyptol, 5 parts,
Medicinal liquid vaselin, 20 parts.
M.

Equal parts of eucalyptol and liquid vaselin may be used, and injections of a syringeful night and morning never cause any local irritation.

Inhalations of sulphurous acid are sometimes of benefit in phthisis. A quantity of sulphur is burned in a confined apartment (20 grammes per cubic metre), and, after waiting twelve hours, the patients are admitted, and made to sojourn in this room several honrs. "Under the influence of this treatment, we observe a speedy change in the expectoration, the cough diminishes, and the patients sleep much better."

These inhalations are not contraindicated in hæmoptysis.

CHAPTER IX.

ON ANTISEPTIC PLEURAL MEDICATION.

GENTLEMEN: In the last chapter I stated the basis on which henceforth antiseptic pulmonary medication should be founded, and in that connection I insisted particularly on the importance of the antimicrobic treatment of tuberculosis; to-day, in order to complete the subject, I wish to say a few words about the application of the antiseptic method to pleural affections; this will be the subject of this short lecture.

Two quite modern methods of a surgical order have profoundly modified the treatment of pleural affections, viz.; aspiration and pleurotomy.

Since Dieulafoy, by his invention, rendered easy for us the method of aspiration, one of the first applications of this method was addressed to pleuritic effusions, and for the first few years it was the custom to puncture and aspirate in all cases of pleuritic exudation, small as well as large. Physicians were heard to maintain, as did my regretted master, Behier, that we ought by an early aspiration to withdraw the liquid from the chest as soon as the physical signs enable us to recognize the least effusion.

This enthusiasm of the onset was not allayed till Ernest Besnier showed us, by figures that could not be gainsaid, that the mortality of pleurisy since the

practice of aspiration was introduced, instead of being lessened, was increased. While recognizing that in this increase of mortality there is doubtless another factor, namely, a greater intensity of the disease, good clinical observers nevertheless regard it as probable that the abuse of aspiration punctures may have had a share in this result. Those who adopted this view based themselves principally on the ideas which to-day dominate surgery; I allude to the possibility of the penetration of certain micro-organisms by the punctures. So, in order to render this little operation free from all danger, it was proposed to perform it according to the strictest rules of antiseptic surgery, and hence we have seen Débove subject the trocars and needles of the Potain aspirator to heat of above 100° C. before using them.

The complication of this latter manœuvre has rendered aspiration somewhat more difficult, but whether this preliminary measure be carried out or not, it is the rule to-day to wash all parts of the Potain aspirator with strong solutions of phenic acid, and to carefully fire the trocar by dipping it in alcohol and setting fire to the alcohol; finally, to use carbolated vaselin to grease the instrument with.

But the antiseptic method has been especially applied to pleurotomy, and it must be conceded that it has in many points modified this operation. But, before describing these modifications, I wish to say a few words about a little harmless measure which will

enable you to recognize the reality and the nature of a pleural exudation; I refer to the employment of your hypodermic syringe.

When you are in doubt as to the presence of an effusion or its nature, it will be sufficient to make with your syringe a puncture in the pleural cavity through an intercostal space, and then draw up a syringeful of liquid—provided there be any liquid there. This aspiration will give you useful information, and it can cause the patient little pain and can do him no harm whatever.

Since Moutard Martin taught us the rules of pleurotomy, this operation has been one of ordinary practice, and I have already shown in the second volume of my Clinical Therapeutics the marvellous results which may be obtained from it, citing the statistics of the surgeon who, out of 70 cases of purulent non-tuberculous pleurisy, obtained 57 cures. Bear in mind that with reference to these purulent tuberculous or non-tuberculous pleurisies, we have to-day a sure means of verifying our diagnosis, and thereby establishing a sure prognosis. I refer to the finding or not finding of tubercle bacilli in the purulent effusion.

I cannot, in this chapter, trace anew all the steps of the operation, for the details of which I shall have to refer you to the work above mentioned. I shall here only point out the modifications which have recently been made in the operation, to the sum of

which has been given the name of antiseptic pleurotomy.

But whether it be antiseptic pleurotomy or pleurotomy as it was formerly practised, with which we have to do, it is a certainty that the operation can be performed to-day almost without pain. You know that in consequence of our not being able to chloroform patients on whom pleurotomy is performed, we have been advised to employ local anæsthesia in the form of ether spray, but this way of obtaining anæsthesia has the disadvantage of determining severe pain when reaction sets in, and of provoking hæmorrhages, which are sometimes profuse and quite difficult to arrest.

To-day we are in possession of a means which enables us to complete all the steps of the operation without pain. It is, as you will readily guess, hydrochlorate of cocaine. I have just applied this method, and with perfect success, on two of my patients on whom I have operated for empyema. This is my mode of procedure: I have at hand a two-per-cent. cocaine solution; I trace out with a pencil a line which I am to incise, and I introduce the needle of my hypodermic syringe successively at both extremities of this line, and throw into the cellular tissue two injections, and I take care, by pressure with my finger, to spread the liquid as thoroughly as possible over the region which my bistoury is about to traverse. I wait five or six minutes, and proceed to the incision of the tissues.

The cutting is absolutely painless, and it is not till you have reached the deep parts of the inter-costal space that any pain whatever is felt, and this is slight.

You will then be likely, henceforth, to resort to this simple expedient under such circumstances; and, since I am on the subject of subcutaneous injections, permit me to say that you can, by the same means, allay the fits of coughing, so painful and so fatiguing, which the patient experiences when you have given exit to an effusion, but this time it must be morphine, not cocaine, which you inject. It is a good plan to have this injection ready and inject it as soon as the pleura is incised, and the patient begins to cough.

I come now to the more important part of this lecture, namely, antiseptic pleurotomy.

Empyema, whatever may be the mode of treatment employed, can end in cicatrization and restoration *ad integrum* only by the jutaxaposition of the two contiguous layers of the pleura, and this jutaxaposition can be effected only by the lung being maintained in contact with the costal parietes which remain fixed, or by the continued application to the pulmonary pleural surface, the lungs being more or less confined to the vertebral column—of the supple and elastic costal wall. From this first fact two important prognostic conclusions result; first, the more movable the costal wall, and the more recent the false membranes, the greater the chances of cure. In accordance with this first conclusion we explain the al-

most constant recovery of young children from purulent pleurisy, and the increasing rarity of recovery as the patient advances in years.

Estlander, by a bold and ingenious process, has proposed to remedy in aged patients the evil alluded to by resection of the ribs, and thus opposing a mobile wall to the pleural abscess. In France, Bouilly, Perier, and Berger, have resorted to this operation with more or less or success. I say more or less, because in the two cases which I was enabled to observe, there was a considerable amelioration, but the patients remained ever afterwards subjects of a pleural fistula.

Nevertheless, by the side of these partial successes, it is but fair that we should mention the brilliant results which this operation has had on one of our most talented and brilliant surgeons, who to day owes to it his complete restoration.

The second conclusion pertains especially to the lungs, and we ought whenever possible to open the pleural abscess before the organization of false membranes has fixed the lung to the vertebral column by firm and resistant bands. Therefore all physicians and surgeons who have counselled antiseptic pleurotomy have insisted that it should be done early—that is to say, as soon as the presence of a purulent effusion has been satisfactorily determined. This is a condition essential to the success of the operation, as in these cases you can obtain, so to speak, reunion of the costal and pulmonary pleuræ by first intention.

It is essential then, in order that the operation may give the results which we have a right to expect from it, that is to say, complete and permanent cure of the empyema in a space of time varying from three to five weeks, that we have young subjects to deal with whose thoracic walls are supple and elastic, or at least that we have to do with empyema at its onset. When, on the contrary, you open the pleural abscess at a very late period, or when your subjects are aged people whose costal cartilages are ossified, the antiseptic method is no longer applicable, and you ought to resort to the ancient mode of operating; and even then there will always be reason to fear that the patient will carry a discharging pleural fistula the rest of his life.

The rules of antiseptic pleurotomy have been well laid down in France by Débove, Lucas Championniere, and especially by my former pupil and present colleague, Dr. Moizard, who is one of the most earnest advocates of this form of pleurotomy. You will find, moreover, in a work published by Hache, and in the theses of M'lle Kraft, Guinard and Le Couédic, all the material needful for the study of this question.*

* Moizard, De la pleurotomie septique et antiseptique (Revue des maladies des enfants, 1884), Mlle Kraft, Traitement de l'empyème par la pleurotomie antiseptique (Thèse de Paris, 1884, p. 153). Guinard, Du meilleur mode de traitement de la pleurésie purulente (Thèse de Paris, 1884). Le Couédic, De la pleurotomie antiseptique (Thèse de Paris, 1885).

These rules consist in performing the dressings according to the most minute requirements of antiseptic surgery; the operation should be done in a Listerian atmosphere; all the sponges and drainage tubes must be soaked in a strong solution of carbolic acid; and when once the operation is terminated, Lister's dressing should be employed in its entirety—that is to say, protective, phenicated gauze, mackintosh, salicylated wadding, etc. As a free and complete flow of pus is desired, it is the rule in these cases to make the incision as low down as possible—that is to say, just above the upper border of the seventh rib. The incision is made as in the ordinary operation, layer by layer, and care is always taken to follow the upper border of the rib below. When once the pleura is opened, the operator introduces his finger into the pleural cavity, and, with his finger as his guide, he enlarges the opening into the pleura with his probe-pointed bistoury.

When once the pus is evacuated, you wash out the pleural cavity with a saturated solution of boracic acid, continuing the irrigation till the liquid returns perfectly clean from the chest. Some surgeons recommend that the first lavage be followed by a second made with a solution of chloride of zinc or corrosive sublimate; I do not see much advantage in this second washing, and I never resort to it. But among the antiseptic solutions which are put into usage, there is one which you ought absolutely to discard; I

allude to carbolic acid. You have had opportunities to see in my hospital service the disastrous results produced by these carbolized lavages of the pleura, which have produced a veritable poisoning, with refrigeration, and grave symptoms which have hastened the end of the patient.

You then place in communication with the purulent cavity a drainage tube, which you have taken care to fasten by a string or tape passed around the waist. *A propos* of these drainage tubes, you know that I employ a flute-like arrangement constructed by Galante, called the *flute of Pan*, which consists of a series of drainage tubes cut at different lengths, and kept in position by a disk which closes the opening into the chest.

This flute of Pan, applicable to the ordinary cases of pleurotomy, is not adapted for antiseptic pleurotomy, and you will have to be content with a large drainage tube, or it may be a series of drainage tubes, which you leave in the opening you have just made, but which you must have care to fix firmly by passing through them a stout thread which is made fast to the chest; the necessity of this is apparent from the fact that a certain number of cases are on record where these drainage tubes, owing to the efforts of respiration and the movements of the patient, have fallen into the pleural cavity.

You then apply over the whole a complete Lister dressing, which you cover with a certain quantity of

wadding; then (and this is the capital point) you disturb the dressings but rarely, and, what is essential, you refrain from further washing out the pleural cavity. It is not till three or four days after, and according as the patient is more or less inconvenienced by the liquid which flows from the chest (unless, indeed, the pus earlier takes on a putrid odor) that you remove the old dressing and put on a new one, which in its turn is designed to be left on for three or four days. It is understood that each of these dressings should be made in a carbolized atmosphere, and with all the precautions of the antiseptic method. At each dressing you remove the tube, and you take care to shorten the drainage tube as fast as the cavity contracts.

In following these rules, if you have a patient who fulfills the conditions which I have enumerated above, you may expect to obtain a definite cure, and without fistula, in a space of time which varies from three to five weeks. If you will take the trouble to refer to the statistics, those, for instance, furnished by M'lle Kraft, you will see that out of 19 cases of pleurotomy in the adult, in 12, where the pleurotomy was followed by repeated lavages, there were two deaths, while in the seven cases treated by only one lavage, there were seven recoveries. Hence this lady claims that the operation for empyema by early pleurotomy, rendered completely antiseptic and followed by only one lavage, is an operation of so little gravity that

one may resort to it with almost absolute certainty of cure.

I fear that this is a complete over-statement of the case; the one lavage which plays the most important part in antiseptic pleurotomy, entails a result which does not at all depend on the method employed, but rather on circumstances inherent in the patient himself, and whenever the pus becomes fœtid, all the advocates of this method recommend to return to repeated washings of the pleural cavity with antiseptic liquids as we were formerly in the habit of doing.

When recognizing that antiseptic pleurotomy ought always to be applied at the onset of empyema, in order that cicatricial union may be obtained of the pus cavity, which is an immense advantage, it must be admitted that in a great many cases this union is impossible, and that the best be can do is repeatedly to wash out the pleural cavity. Such are the points to which I desire to call your attention concerning antiseptic pleural medication.

CHAPTER X.

ON ANTITHERMIC MEDICAMENTS.

Gentlemen:—I intend to-day to begin the study of antithermic medication, and shall devote to it the three following lectures. In the first I shall consider the antithermic medicaments which have been in vogue down to the last few years. In the second I shall take up the study of resorcin, antipyrin, kairin, and thallin. In a third and final lecture, I shall examine the indications and contra-indications for the antithermic medication.

Since the year 1834, when Runge first extracted phenic acid from coal tar, chemists have obtained by analyzing the residual products of the fabrication of coal gas derivatives of a constantly increasing importance, so that we may now say that this illuminating gas, which was formerly considered as the most important element in the destructive distillation of coal, is now regarded from an industrial point of view as only a secondary product. The coloring matters, anilin and its derivations, the phenols and oxyphenols constitute, in fact, to-day one of the most important branches of the chemical arts.

Medicine has largely profited from this group of bodies, early finding there medicaments that are powerfully antiseptic. Then, when clinicians ventured to make trial of these medicaments internally,

it was observed that all, or almost all, have the curious property of depressing the temperature in a very marked manner, and this has enabled us to construct a new class of remedial agents, the antithermic medicaments.

But in order that you may well grasp the intimate action of these various medicaments, it seems necessary for me to sum up in a few words the various hypotheses that have been made respecting fever and hyperthermia in general.

Fever, as you know, is essentially characterized by two cardinal symptoms: Augmentation of the pulse, and augmentation of the heat. Since the introduction of the thermometer into the study of diseases, the second of these symptoms has become of increasing importance, and to-day we relegate the study of the pulse to an absolutely secondary rank. It is, then, this hyperthermia which constitutes the characteristic, dominant fact of fever, and from this it borrows its name (*febris*, from *fervere*—"to glow with heat, to boil.")

Many theories have been put forth to explain this febrile hyperthermia, and when you take a general view of them, you see that they can all be grouped in two great classes, in the one, physiologists have hypothecated an augmentation of the combustions of the economy; in the other, on the contrary, this augmentation of combustions is not admitted. To-day, despite the recent experiments of

Charcot, and those more recent still of Maurel, everybody is agreed in admitting that there is this increase of combustions, and if there be any contradiction in the results obtained on this point by different physiologists, it is because the latter did not place themselves in the same conditions of experimentation.

You know, gentlemen, the most expeditious and clinical means for determining the activity of combustions taking place in the economy. I refer to the quantitative analysis of the urea. In order that you may appreciate by this process the increase of combustions in febricitates, you must compare the quantity of urea excreted in twenty-four hours by a fever patient, not with that excreted by a man who is on full diet, but with that eliminated by a person fasting, since febricitates take little or no food. When this kind of comparison is made, it is seen that there is always augmentation of urea production in fever.

Moreover, the experiments of Liebermeister show that there is also augmentation in the carbonic acid exhaled. Lastly, the application of calorimetry proves in a sure manner that the febricitate evolves more heat than the healthy man, and that the production of heat is in direct relation with an augmentation in the chemical combustions in the organism. Therefore the theories of Traube and Hunter, who teach that febrile hyperthermia is due solely to modifications in the capillary circulation, ought to-day to be abandoned.

But to say that fever is due to augmentation of

the combustions of the economy, is not to solve the problem, but simply to remove it farther back; hence, physiologists have tried to penetrate more deeply into the matter. First of all, Leibermeister has shown us that in fever there is modification in the regulation of heat. What is this organic power of heat regulation? It is this: We can by artificial means augment the temperature of the organism, but as soon as these means cease to act, the bodily temperature always comes back to the normal, *i. e.* to 37° C. Hence, then, man in the physiological state tends always to maintain his temperature about a uniform standard, while in fever the bodily heat is regulated by an abnormal standard.

This study of the relation of the temperature in fever is important, but it does not absolutely resolve the difficulty, and we ought to know how this abnormal regulation comes about. Here two great causes have been invoked: Some would place in the nervous system the starting point of this trouble; others have located it in the blood; in other words, we have the nervous theory of fever, and the humoral theory.

Basing himself on his remarkable experiment of the section of the great sympathetic in the hare, an experiment which, as you know, leads to a very marked augmentation of temperature in the ear on the side where the nerve was cut, Claude Bernard inferred that the great sympathetic is the moderator of the chemical combustions of the economy, and fever was, in his

estimation, but one of the manifestations of paralysis of this portion of the nervous system. Tsheschichin in acting on the pons varolii of hares, determined augmentation of the temperature of the body, and hence located in the mesocephalon the heat centre of the economy. Vulpian does not acknowledge as the special seat of calorification either the great sympathetic or the mesocephalon, but he thinks that every modification effected in the nervous system, whether by direct or indirect causes, may influence the combustions of the economy and thereby produce fever. So much for the nervous theories of fever. As to the humoral theories, every one is agreed in admitting the prominent part belonging to the blood in the febrile process. But some affirm that the blood-disorder is primary, others that it is only secondary. The study of new antithermic medicaments has not enabled us definitely to decide this question. On the contrary, you will see that if there are medicaments which depress the temperature by acting on the nervous system, there are still others which produce the same effect by profoundly modifying the blood globules.

Taken in their aggregate, the antithermic medications may be divided into two groups. In one the temperature is lowered by abstracting, through physical means, the heat which is generated by the phenomena of combustion taking place in the economy; in the other, it is by acting directly on the blood

or on the nervous system that this heat-fall is produced.

The first group is typically represented by the cold bath treatment of pyrexia. You will allow me to be brief on this head; this question has been recently discussed at length before the Academy in connection with the treatment of typhoid fever by the method of Brandt, a discussion in which I took an active part; and I have, moreover, stated in the third volume of my Clinical Therapeutics * what I think of this method. Events which have since taken place have in no way shaken my conviction, and I persist in believing that the employment of the cold bath as an antithermic, and in particular in the treatment of typhoid fever, is destined to be virtually abandoned. Moreover, to abstract heat from the economy by physical means does not in any way oppose heat production.

I come now to the second group of antithermic medications, and what I have to say to-day will pertain to certain members of this group. These medicaments are subdivided into two classes; those which act directly on the blood, and those which act on the nervous system.

Among the medications which directly influence the blood, must first be mentioned blood-letting. If formerly the medical profession urged and applied with so much rigor the antiphlogistic method, it is because it produced in inflammatory diseases and in

* Published by Geo. S. Davis, Detroit, 1888. Part III.

pyrexia the following double effect: It raised the pulse and lowered the temperature; in a word, it combated one of the most perceptible manifestations of inflammatory diseases—the fever.

Consider what takes place in the course of typhoid fever when there ensues an intestinal hæmorrhage of medium intensity. The temperature falls almost immediately, and on the fever chart you see this hæmorrhage marked by a notable depression of the temperature, which is continued on the following days—a depression absolutely like that produced by the administration of an antithermic medicament, such as sulphate of quinine, salicylic acid, salicin, etc.

I pass now to the study of the internal medicaments capable of lowering the temperature, but before giving a more complete account of those later antithermics, kairin, thallin, resorcin, and of those which preceded them in the order of their discovery, such as phenic and salicylic acids, I ought to say a few words about two medicaments long employed in fevers and phlegmasias: I refer to tartar emetic and quinine.

Tartar emetic is a powerful antiphlogistic, and, like blood-letting, it depresses considerably the temperature, determining an aggregate of symptoms very similar, from a thermic point of view, to what we see manifested in the third stage of cholera, whence the name of *stibian cholera*, which has been given to this symptomatic aggregate. Such a depression was not to be obtained without danger, and numerous were

the observations during the time of furor for the administration of tartar emetic, where irremediable disorders on the part of the digestive tube were noticed. To-day the antiphlogistic medication by tartar emetic is pretty well abandoned, and you will see as I go on that we possess means far more energetic and far less dangerous for bringing down the temperature.

If quinine remains still the medicine *par excellence* for morbid intermittency, and for fever and ague, it has shown itself inferior as an antithermic to the medicaments of which I am about to speak. To obtain appreciable antithermic effects in pyrexias, one is obliged to give large doses of quinine; and, as Broqua of Mirande remarked in 1840, and still later Boucher of Villijosy, and Monneret, when you wish, in typhoid fever for instance, to bring down the temperature by sulphate of quinine, it is by grammes or scruples rather than by grains that you must administer it. These massive doses of quinine are not without danger; besides the encephalic disorders which they produce, there are sometimes engendered under their influence, as Laborde has shown, grave cardiac lesions characterized by a veritable myocarditis, such as is often developed in typhoid fever and other infectious and virulent diseases, as has been noticed by Huchard, Desnoy, and Hayem.

How does quinine act in depressing the temperature? Two hypotheses have been invoked. According to the one, the cinchona alkaloids have an anti-

septic action, and in this way they oppose fever which is essentially a fermentation; it is, moreover, worthy of note, that a great number of antithermic substances are antagonistic of fermentation. What I say of quinine I may also say of phenic acid, salicylic acid, resorcin, etc.

The other hypothesis, much the more probable, is that the salts of quinine depress the temperature by acting directly on the thermogenetic centres of the cerebro-spinal axis. The effects of quinine on the nervous system are not at all doubtful, and the buzzings in the ears, the attacks of vertigo, and the cardiac disturbances sufficiently indicate that the cerebrum, and especially the upper parts of the cord where the heat centres have been located, are impressed by the salts of quinine.

I ought not to omit digitalis, which not only diminishes the number of the pulsations, but has a manifest action on the temperature. Hirtz and his followers have long insisted on the antithermic, or rather on the antipyretic value of digitalis which they have administered in the pyrexias, and especially in typhoid fever. This method of treatment which Wunderlich advised as early as 1862, and which Hirtz tried in France in 1869, consisted in giving to typhoid fever patients hourly doses of a tablespoonful of an infusion of 12 to 15 grains of digitalis leaves in a gill of water. Save the case of the followers of Hirtz who have continued this treatment, it seems to have

been almost completely abandoned, and I believe that this abandonment is justified, for the reason that digitalis is a dangerous antithermic medicament by reason of its emeto-cathartic action, and its liability to paralyze the heart in the large doses required in order to bring down the febrile heat.

In fact, in the dose of 15 grains a day digitalis may produce toxic effects, and bring about a veritable asystolia, and this is the more likely to ensue from the fact that in typhoid fever, as in other infectious diseases, the heart, as we have just seen, is softened in its muscular texture.

It is on account of this same debilitating action on the heart that we should discard from the antithermic medication aconitia and veratriinum; these medicaments indeed depress the temperature, but in order to obtain this effect we have to evoke the toxic action of these alkaloids, and this is likely to be attended with dangerous results. It is not so with the medicament which I am next to mention, salicylic acid, which belongs to the aromatic series from which are derived all the antipyretics whose uses I am about to set forth.

Salicylic acid was the first medicament of this series to be applied to the treatment of pyrexias. The first experiments with this acid were made in 1874, by Bass, and one year later (1875) Reiss prescribed it in typhoid fever. This was a partial return to the first uses made of salicin, which was dis-

covered in 1827 by Leroux, of Vitry-le-Francois, and which was for a time administered in fever and ague. The year following (in 1876) Stricker made trials of salicylic acid in acute rheumatism, and founded the principles of the salicylic medication, which gives every day such remarkable results in this painful affection.

Salicylic acid is antithermic, and the most active and least dangerous medicine of the kind. To bring down the temperature with salicylic acid, pretty large doses are requisite, of the acid or of salicylate of soda, and from an antithermic point of view the first is far preferable to the second.

You must, as I said before, administer 1, 2, 3, 4, and even as much as 7 grammes a day in powders of one-half gramme every hour. This is Vulpian's and Hallopeau's way of giving it, who are very earnest advocates of the salicylic medication in typhoid fever.

The physiological effects of salicylic acid are very similar to those of sulphate of quinine, and it is probable that it is by acting on the thermogenetic nervous centres that salicylic acid brings down the temperature. But the same evils which we have ascribed to quinine when given for antipyretic effect apply to salicylic acid. The cerebral disturbances which the latter occasions are quite as annoying and as harmful as those of quinine, and despite the power which salicylic acid possesses as an antithermic, I am persuaded that if it occupies the first rank in the thera-

peutics of acute rheumatism, it deserves but a secondary place in the treatment of febrile hyperthermia; as for its action in intermittent fevers, this is well nigh *nil.*

Phenic acid was employed in fever before salicylic acid, but it was not till after the year 1880 (that is to say, since the labors of Desplats of Lille,) that any real scientific trials were made with it in fevers, and in typhoid fever especially. Skinner in 1873 did indeed advise phenic acid in the treatment of fever; Pecholier in 1874, and Tempeste in 1877, had also administered it; but all in such feeble doses that it is hardly probable that it was for an antipyretic effect that it was exhibited.

Phenic acid is a very powerful antithermic, and we have seen relatively small doses of thirty grains produce a fall of several degrees. These falls of temperature are accompanied by grave symptoms; the skin is covered with sweat, the respiration is oppressed, there is a general depression of the forces of the economy, all of which symptoms render phenic acid a dangerous medicament, for it owes its antithermic effects to its action on the nervous system and on the blood globules. It is, in fact, by diminishing the respiratory power of the blood, that phenic acid depresses the temperature, and we ought to banish from therapeutics those sanguineous antithermics which notably augment the blood alterations which characterize all the infectious pyrexias. Hence it is

that phenic acid as an antithermic is to-day abandoned, and for this reason that we have found antithermics just as powerful which are attended with far less danger. This is a matter which I hope to show you in the next lecture will be devoted to the new antithermic medicaments.

CHAPTER XI.

ON NEW ANTITHERMIC MEDICAMENTS.

Gentlemen:—In my last lecture I spoke of the antithermic properties of quinine, phenic acid, and salicylic acid. To day I shall conclude the subject by a brief reconsideration of resorcin, kairin, antipyrin, and thallin.

Resorcin, which two Vienna chemists, Hlassiwetz and Barth, discovered several years ago among the products of fusion got by treating galbanum with potash, has since then been obtained by Köerner by way of synthesis, and to-day makes a part of the group of phenols. It presents itself when pure under the aspect of beautiful silk white needles, very soluble in water, and gives rise, like salicylic acid, to a remarkable violet coloration in presence of perchloride of iron. In contact with sulphuric acid and phthallic acid it gives origin to *fluorescin*, of which several drops suffice to render water singularly fluorescent. From this combination with phthallic and sulphuric acids results a variety of beautiful colors, which cause resorcin to occupy an important place in the fabrication of coloring matters. This substance is eminently antagonistic to putridity and fermentation. Since 1877, Dr. Andeer, who has studied the question of resorcin under all its phases, has made known the numerous applications which may be made of this

body in therapeutics, and I myself, in 1880, was the first to make trial of this medicament in France, and you will find in the thesis of my pupil, Dr. Callias, the results of our researches.*

The analogy which exists between resorcin and phenic acid led to the use of the former in fevers, and especially in typhoid fever.

In Germany there has been much said in praise of resorcin as an antithermic. Licehthein affirms that when administered in a massive dose of 30 to 60 grains it causes a very marked fall of temperature in typhoid fever. The observations which I have made have not given me results so advantageous, and neither in articular rheumatism nor in typhoid fever have I observed any considerable fall in the temperature. It is

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* Hippocrate Callias, De la résorcin et de sou emploi en therapeutique (Thèse de Paris, 1880). Dujardin-Beaumetz, Bulletin de thérapeutique (June and July, 1881). Revue de Hayem, 15 Jan , 1881, No. 62. Ramonet, Traitment de la fièvre typhoïde par l'acide phénique (Archives de médecine de April, 1882). J. Andeer, Eilenten Studien uber das Resorcin zur Einführung desselben in die praktische medicin, Wurtzburg (A. Stubdr's Buch et Kunstahlung, 1880). Lichthein, Blätter für Schweiger Artzfe (Correspondanz, No. 14, 1880, Tribune méd., Nos. 628 et 630, 1880). Dr. W. Murrel (of London), a Case of Poisoning by Resorcin (Medical Times and Gazette, 22 October, 1881, p. 486). Dubois-Raymond, Archives de 1879. Supplément B. D. S., 61; L. Brieger zur Kenntniss des physiologogischen, Verhaltens des Brenzcatechtn, Hydrochinon und Resorcin und ihrer Entstehung im Tierkœrper.

true that I gave the resorcin in fractional doses of 8 grains without ever exceeding the total quantity of half a drachm a day.

My colleague Desnos has repeated at the Charity these experiments to ascertain the antithermic powers of resorcin, and the results at which he has arrived, and which you will find recorded in the thesis of Dr. Peradon, confirm in part the conclusions which I had formulated. He has in fact remarked that resorcin has almost no action when administered internally in acute rheumatism, but in typhoid fever, when it is given in massive doses of from half a drachm to a drachm repeated two or three times a day, so that from a drachm and a half to two drachms shall have been given in the twenty-four hours, you obtain a real fall in the fever, but the action is very transient.

But what led me to abandon resorcin in the treatment of rheumatism and typhoid fever is not only its want of power, but also the toxic phenomena which I have observed. Resorcin is not only an irritant medicament, it is also a poison, and in the experiments which I made with Callias, we found that when we arrived at the dose of 30 centigrammes for each kilogramme of the weight of the body, we determined in the dog convulsive phenomena, and death when the dose reached 90 centimetres per kilogramme of weight. In the animals which succumbed to the effects of resorcin we noticed visceral congestions,

and in particular very intense pulmonary congestions, as in the case of animals poisoned by phenic acid.

Man seems more susceptible to the action of resorcin than animals. Murrel has observed a case where 50 grains of resorcin administered in one dose determined grave symptoms of poisoning, from which the patient, however, recovered.

Hence, while recognizing that resorcin is less toxic than carbolic acid, I conclude that it is a dangerous antithermic, for I found in my patients affected with typhoid fever and treated by resorcin, the same depression of the forces, the same adynamia, the same pulmonary congestions, which I had signalized in those to whom carbolic acid had been administered. I have therefore abandoned this medication, and I believe that even in Germany resorcin is little employed internally; it remains, on the contrary, a precious medicament for external use in the treatment of ill-conditioned wounds.

Kairin, which Fischer, of the University of Munich, discovered in 1882, was applied to therapeutics by Filehne, of Erlangen, and has been especially studied in Germany by Guttmann, by Gottlief Merkel, and in France by Dr. Hallopeau and his pupil Dr. Girot, who has devoted his inaugural thesis to this subject.*

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* Guttmann, Berliner Klinische Wochenschrift, No. 31. Gottlief Merkel, Deutches Archiv. für Klinische Medicin. Filehne, Berliner Klinische Wochenschrift, 16e numéro.

Kairin is a derivative of quinolin; it is the methyluret of oxyquinolin. This quinolin, as you know, has but one very remote point of contact with quinine. It was obtained from coal-tar by Runge in 1873. Gerhardt obtained it by distillation of certain alkaloids—quinine, strychnine, cinchonine, with potassa—and the derivatives of this quinolin have been especially well studied in France by Œschener of Coninck.

I shall not enter into this very complex and purely chemical question of the quinolin series and of its derivatives; this I leave to my laboratory chief, Dr. Bardet; it is sufficient that I should tell you that chlorhydrate of kairin presents itself under the form of a crystalline powder of a straw-yellow color. Its price is relatively high. It is soluble in water, and its solution has a bitter and disagreeable taste. Hence it is that it is administered in wafers or capsules.

Filehne advises to give every hour one of these wafers containing half a gramme of kairin-chlorhydrate. At the end of four doses—that is to say, at the end of four hours—the fever-fall is two or three degrees. Under the influence of these doses the patient sweats, feels depressed, and his urine takes on a black

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Girat, Contribution à l'étude physiologique et thérapeutique du chlorhydrate de kairin (Thèse dé Paris, 1883, No. 230). Hallopeau Sur un nouvel antipyrétique, le chlorhydrate de kairin (Soc. med. des hôp., 23 mars 1883, et Bull. de thér., 1883, t. civ, p, 241).

color, like that of individuals who have taken large doses of phenic acid. When the administration of the kairin is stopped, the patient rapidly recovers the temperature which he had before taking the medicine, and this new thermic elevation is preceded by an intense chill.

The transient duration of the antithermic action of kairin, and the production of the chill, is not the only inconvenience of this medicament. There is a much more series evil resulting from it, for kairin acts on the red globules and on the oxyhæmoglobin, which it destroys. In their experiments on animals, Hallopeau and Gèrard had noted a modification in the color of the blood, which took on the color of sepia, and they had remarked numerous sub pleural ecchymoses.

These accidents always occur when too large doses of kairin are administered, and it is a medicament which causes the death of a dog when doses are given which equal one gramme per kilogramme of the weight of the animal.

Kairin is then an antithermic substance, but one which acts by diminishing the respiratory power of the blood, and by destroying the hæmoglobin. In some recent researches, Brouardel and Paul Loye have confirmed this view, and have shown that thallin and kairin have a similar action—that of destroying the hæmoglobin. Moreover, contrarily to what takes place in the case of the other antithermics, kairin and thallin have no action on the fermentations.

Kairin then ought to be discarded from therapeutics. It is a dangerous medicament, because it produces its antithermic effects by destroying the hæmoglobin and by profoundly altering the blood—circumstances which should be especially avoided in the infectious febrile diseases.

Thallin has many points of contact with kairin, belonging, like it, to the quinolin series. It is the tetrahydroparamethyloxyquinolin. I do not know what is the value of this chemical appellation, but protest against any such barbarous scientific nomenclature. The name of thallin (*thallus*—"a green brach") was given to it by Skraup, its discoverer, by reason of the emerald-green color which it assumes under the influence of perchloride of iron.

The sulphate and the tartrate of thallin are the salts in medicinal use. The sulphate is very soluble in boiling water, and in five times its weight of cold water. Thallin, as has been shown by Jacksch, of Vienna, lowers the temperature in the dose of from 25 to 50 centigrammes, and this without provoking sweating.* Huchard has confirmed these facts, and I have myself been able to observe the antithermic action of thallin. Unhappily, thallin, like kairin, lowers the temperature not by acting on the thermic centres, but by diminishing the respiratory power of the blood and dissolving hæmoglobin, and the researches of

* Huchard, Sur un nouvel antipyrétique: la thallin (Union Médicale, No. 2, Jan. 3, 1885, p. 13).

Brouardel and of Paul Loye seem to us demonstrative of this fact.*

Thallin is the most powerful of antithermics, and we have seen Jaccoud, with doses of one gramme administered every half hour in divided doses during the 24 hours, obtain, in a tuberculous patient, a fever-fall of five degrees, so that the temperature of the patient was reduced to 32.4°, and strenuous efforts were required to arouse him from the state of collapse into which he was plunged. It is necessary, then, to give it only in very small doses of not more than four grains.

As in the case of kairin, it is to a chemist of Munich, Ludwig Knorr, that we owe the discovery of antipyrin, and, again, it was Filehne, of Erlangen, who was the first to experiment with it. The chemists are not yet agreed as to the exact name which we ought to give to antipyrin. Some think that it should be called *dimethyloxyquinizin;* others, on the contrary, call it *methylated oxymethylquinizin.*

Antipyrin presents itself under the form of a reddish-gray crystalline powder, very soluble in water, and with a slightly-bitter savor, which is not unpleasant to the taste. It may be given by the mouth, by clysters, or by hypodermic injections. When given by the mouth, it is in sweetened water, rendered

* Dr. Rudolf von Jacksch, assistent der Medizinische Klinik in Wien, Thallin, ein neues antipyreticum (Wr. Med. Wochenschr., No. 48, 1884).

aromatic by a little peppermint or lavender, that you can best prescribe this medicament.

The physiological and toxic actions of antipyrin have been well studied in France and in foreign lands. In France it was Huchard who was one of the first to make known to us the therapeutic and toxic use of this substance, and you will find in the thesis of his pupil Arduin the principal facts resulting from this study.*

Antipyrin is toxic, but it is much less so than resorcin, which again is less toxic than phenic acid; and while it takes less than one gramme of resorcin per kilogramme of weight to kill a hare, more than 1½ grammes of antipyrin is requisite to produce the same fatal effect. The symptoms of poisoning are, however, almost alike in both cases; these are of tetanic and paralytic character, exactly resembling those which characterize strychnine-poisoning. It is not, then, doubtful that antipyrin acts on the cerebro-spinal axis, and it is probable in modifying the thermogenetic centres that it depresses the temperature.

This medicament has little action on the circulation. Some affirm that it augments the arterial tension; others, on the contrary, that it lowers it; but everybody is agreed in recognizing the little influence that it has on the number of the pulsations. But, unlike kairin, it does not seem to modify the blood, and

* Arduin, Contribution à l'étude physiologique de l'antipyrin (Thèse de Paris, Feb., 1885).

in particular the hæmoglobin. In fine, always, with reference to this action on the circulation, do not forget to note the curious hæmostatic effects which Henoque has attributed to antipyrin — a hæmostatic action which seems to be superior to that of ergotin and perchloride of iron. It is well to remember this fact *à propos* of the treatment of certain hemorrhages, and in particular of hæmoptysis.

Antipyrin is eliminated by the kidneys, and this elimination is easily recognized by the aid of perchloride of iron, which gives rise to a reddish-purple color in the urine. This medicine diminishes the urine; and I have been able to observe this diminution in a patient affected with simple polydypsia, to whom I had administered it. It has also a notable action on the perspiration, which it augments, and this is ever a disadvantage in administering antipyrin to tuberculous patients. In fine, I shall have finished what concerns the physiological action of antipyrin when I have stated that, like the phenols and oxyphenols, it is an antagonist of fermentation.

In what dose should antipyrin be administered? If we follow the precepts laid down by Filehne, we should thus give it: To an adult febricitate two grammes of antipyrin in one dose. This produces at once a fall in the pyrexia of one or two degrees; then at the end of four hours, at the moment when the temperature tends to regain its former height, you repeat the dose of two grammes, then, four hours after, when

the fever again begins to rise, you give one gramme, and thus obtain a thermic depression which may last for 24 and even 48hours. This is the practice first followed in France, but we have had to abandon it in the case of tuberculosis by reason of the profuse sweating which this mode of treatment causes.

Huchard has proposed to diminish the dose to 50 centigrammes, which he would give only every other day. Darenberg gives much larger doses, even six grammes a day, to his tuberculous patients. But this question of dosage is entirely relative to the nature of the febrile process, and I ought, in this connection, to give you more precise information. The study of the new antithermics has, in fact, shown us that, according to the nature of the fever, the hyperthermia presents a variable resistance to the same antipyretics; so that, with an equal temperature of forty degrees in a tuberculous patient and in a typhoid fever patient, 50 centigrammes of antipyrin will cause a fall of temparture in the first, while in the second it will be without effect.

However this may be, we may give antipyrin either in the period of apyrexia, or during the fever. In the first event, we prevent the return of the hyperthermia; this is the practice which Darenberg has adopted, who gives to his tuberculous patients fifteen grains of antipyrin before the onset of the fever, *i. e.*, before the thermometer has attained 37.5° C.; then he gives another dose of 15 grains whenever, in the

course of an hour, the temperature rises more than three-tenths of a degree.

The other method consists in giving antipyrin during the fever. Ordinarily it is at the end of half an hour that the fall is produced, a fall which is generally preceded by a marked sudoral period. At the end of four hours, according to the febrile process, the temperature tends again to rise. Hence it is difficult to lay down precise rules for the administration of this medicament, and it is necessary to depend strictly on the thermic curve, and whenever the thermometer tends to overpass certain limits, say 38,39 and 40 degrees, give a new dose of antipyrin, which should vary, according to the intensity of the fever, from 7 to 15 grains.

At the same time we can affirm with assurance that antipyrin may be given without any harm in fractional doses up to one one and a half and even two drachms in the twenty-four hours.

Acetanilid (Antifebrin).—The introduction of acetanilid into therapeuti s is due to Cohn and Hepp, in 1886, who first made known its antithermic properties, and called it antifebrin. Acetanilid is obtained by the action of glacial acetic acid on anilin. It is a substance of a beautiful pearly white color, of slightly pungent, not disagreeable, taste. Very crystallizable. It is but very slightly soluble in water. Its chem ical formula is C_8H_9NO.

Cohn and Hepp were among the first to test this new antithermic in fevers, and in forty-five cases (typhoid fever, acute rheumatism. erysipelas, septicæmia, etc.) they found that

doses of one-half to one gramme administered every hour till the effect sought was produced, rapidly brought down the temperature several degrees. The digestive system was never disturbed by the medicine. Since then the new antipyretic has been much tested in all parts of the world, and has been found to have effects much like those of antipyrin in about half the dose of the latter. It can hardly, however, be considered a safe antipyretic on account of the cyanoses which it sometimes provokes.

In this country, the profession has had a large experience with acetanilid as a febrifuge, and the verdict has generally been in its favor as against antipyrin; it certainly does not deserve condemnation on the score of greater danger. Moreover, acetanilid is not the product of a *monopoly*, and is cheap. Antipyrin is a patented medicine, and for that reason should be tabooed by the profession, if reliable substitutes not patented can be found.—TRANS.

PHENACETIN.—Discovered in 1887 by Kast and Huisberg. The phenacetins are three in number,—*Orthophenacetin*, *metaphenacetin*, and *paraphenacetin*. The general formula is as follows: $C_{10}H_{13}N.O_2$. Orthophenacetin and paraphenacetin are medicinal.

Phenacetin, like antifebrin and antipyrin, is both antipyretic and analgesic. In five grain hourly doses, like acetanilid, it has been found to produce decided antithermic effects in five patients, the temperature in the course of two or three hours falling two or three degrees. No toxic effects have been noted in connection with its medicinal uses. Like the other antipyretics when given in fevers, it in no way influences the course of the disease.

Phenacetin insoluble in ordinary menstrua, is most conveniently given in tablets or capsules. From extensive trials, it would seem to be as good an antipyretic as antipyrin; it is safer; the dose is one-half less; more expensive than acetan-

lid, it is less so than antipyrin. Thus far the sale of phenacetin is controlled by a patent, a fact to be deplored.—TRANS.

CHLORALAMID.—Chloralamid or chloral-formamid, is a synthetical product derived from chloral anhydrid and formamide; it forms colorless crystals, and is said to be soluble in 9 parts of water and 1½ parts of alcohol. The taste is mild, slightly bitter but not astringent. It is incompatible with alkaline solutions.

Paterson was one of the first to introduce this new drug to the profession as a hypnotic of considerable power. He gave it in 14 cases of insomnia, including simple sleeplessness, and that resulting from phthisis, heart disease, enteric fever, etc. The doses ranged from 15 to 45 grains disolved in warm water with the aid of a little alcohol. The sleep was generally sound and refreshing, with few or no unpleasant after effects. It is especially in the insomnia of phthisis that its influence was found satisfactory. It also had a favorable effect in checking excessive night sweating. It was found not incompatible with organic heart disease. Doses of 40 to 50 grains have sometimes produced some giddiness and stomach sickness. Pharmacists sell this new drug in five and ten grain tablets.—TRANS.

AMYLEN HYDRATE.—Still another new hypnotic has lately been introduced to the profession by Prof. Von Mehring. This substance which goes by the name of *Amylen hydrate* belongs to the group of the tertiary alcohols. It was discovered by Wartz, and is a complex product of the laboratory. It is a clear colorless liquid with a penetrating odor resembling camphor, oil of peppermint and paraldehyd. Von Mehring's first observations were made on sixty different individuals, in doses varying from 3 to 5 grammes. The affections in which he employed it were of the most varied character,—sleeplessness from nervousness, in delirium tremens, phthisis, and in convalescence from various acute diseases. It generally proved

very efficacious. Like chloral, it proved unreliable in sleeplessness due to pain.

It is said to be free from danger, and is more pleasant than either chloral or paraldehyd, though weaker as a hypnotic than chloral. It does not depress the heart or respiratory centres, as chloral does. Since Von Mehring's observations, this new drug has come quite extensively into use. A safe commencing dose is half a drachm.—TRANS.]

Now that you are acquainted with these different therapeutic agents, I shall, in the next lecture, set for the benefits and advantages which you may derive from these different medicinal agents.

CHAPTER XII.

INDICATIONS FOR ANTITHERMIC MEDICATION.

GENTLEMEN: Fever, as we have said, is characterized by an augmention of the pulse and temperature, and we have proved both of these phenomena to be due to an increase of the combustions of the economy. Is this hyperthermia attended with danger, and is it necessary to endeavor to bring back the inordinately high temperature to a lower figure? First of all, you must be aware that to reduce the temperature and to combat the hyperthermia is not to annihilate the fever, nor even to reach the cause which has provoked it. To depress the temperature of a man affected with pneumonia is not to cure the pneumonia. To cause typhoid fever so to undergo evolution that the temperature shall never rise above 38° C. (100° F.), and to maintain the heat-curve on a horizontal line—which is quite possible at the present day, thanks to the antipyretics of which I have spoken, is not to cure the fever; and this is so true that it is a fact that by the employment of the antithermic medication we do not diminish by one day or one hour the duration of the febrile malady. The antithermic medication, then, influences only one of the elements of the fever.

I share in this regard the views of my colleague and friend, Dr. Huchard, who has said that in clinical practice we ought to have no *antithermic* medicaments,

but rather such as are *anti-hyperthermic*, meaning by these words that it is only against the excessive elevation of the temperature, and not against the fever, and the determining cause of the latter, that we should make use of the medicaments whose history I have traced for you.

Has the hyperthermia, then, any danger by itself? Here there have been adduced, in order clearly to set forth the dangers of hyperthermia, three orders of proofs; the first derived from observation of the fever itself, the second from pathological anatomy, the third from physiological experimentation.

1. As for the proofs derived from observation of the fever itself, the German school has maintained that it is to the elevation of the temperature that are to be referred on the one hand the augmentation of the pulse and the increased frequency of the respirations, and on the other, the aggravation in the general symptoms and the delirium; that, in a word, all the grave symptoms of the disease result from the sole fact of the hyperthermia. To give a more certain proof of this affirmation, the German physicians have pretended that it is sufficient to bring down the temperature to cause all these grave symptoms to disappear. There is here, it must be admitted, an evident overstatement; and it seems to me difficult in clinical practice thus to separate the hyperthermia from the other grave symptoms which accompany it. All these phenomena constitute a complete syndrome which

affirms the gravity of the disease; and if the state of the forces is enfeebled. if delirious manifestations supervene, it is not only because the temperature is raised, but also because the general condition is aggravated.

Take a case of infectious pneumonia. You can artificially depress the temperature, but you cannot by that diminish the gravity of the disease, and the patient may even succumb with a temperature almost normal. Observe how it is in typhoid fever; you will see patients who bear their disease very well with temperatures elevated to 40° C. or above, and this without delirium; others, on the contrary, present an ataxo-adynamic state of the greatest gravity, with depression of the forces, despite a temperature very little above the normal.

Even when we interfere with our antithermic medicaments, we obtain a fall of the temperature, it is true; but as we combat only one element of the disease, we do not cause disappearance of the latter, which, according to the type, remains grave or benign. I am well aware that in speaking thus I am setting myself against the views of Brandt and his school, which assert that by employing the method of cold baths from the commencement of the hyperthermia you will reduce all forms of typhoid fever to a similar benign type. Now that we possess antipyrin, which is much more powerful than cold baths to reduce the temperature, we shall be in condition certainly to de-

termine if the statement of the physician of Stettin is correct; but what I can affirm, as a conclusion from the few cases of typhoid fever which I have already treated with antipyrin, is that, while lowering the temperature, this medicament has no influence on the march of the disease.

So then, from a clinical point of view, the hyperthermia is not the sole element of the fever, and it is not correct to say that it holds under its dependence the other grave manifestations.

2. Let us see if the anatomical proofs are more convincing.

Liebermeister and his school have taught that the febrile hyperthermia entails grave lesions in the economy which affect the liver, the kidneys, and in particular the heart and the muscles. These last lesions, as you well know, have a marked importance; it is, in fact, certain that those curious alterations described by Zenk, which pertain especially to the respiratory muscles, as well as the cardiac degenerations, are a frequent cause of death in typhoid patients, but are they indeed the result of elevated temperatures? If it were so, you would understand the importance of actively interfering to combat the elevation of temperature. Unfortunately, there is nothing demonstrative in this respect.

Prof. Hayem, in his interesting researches on the symptomatic myosites,* has shown that it is

* Hayem, Arch. de Phys., Paris, 1870.

especially in the febrile infectious diseases that these profound disorders of the nutrition of the muscular fibres are produced, and that in these anatomical modifications the general empoisonment of the economy plays a more considerable part than the hyperthermia. One may even go further to-day, I believe, and say that the proto-organisms (microbes), which constitute the very essence of these diseases, must be the principal efficient cause of the symptomatic myosites.

Vallin has, however, shown us by direct proof, that in an individual suffering from typhoid fever of apyretic form, and whose temperature never exceeded 37.6° C., there existed a very extensive vitreous degeneration, with ruptures and hæmorrhages of the muscles of the abdomen and thigh, showing conclusively that there are grave typhoid fevers which are almost apyretic. As you then see, the anatomical proofs are not more demonstrative than the clinical proofs. Let us now examine the evidence which physiological experimentation has to offer. This evidence seems at first sight to be convincing.

3. Physiologists have shown that when by artificial means you raise the temperature of the animal, death supervenes when the temperature exceeds by four or five degrees the normal figure. Claude Bernard, in his celebrated experiments made on different animals, has shown that death takes place in the bird when the temperature attains 48° to 50° C.;

in mammals when it reaches 38° to 40° C.; and in cold-blooded animals when the thermometer indicates 37° to 40° C. The toxic scene is almost always the same in animals; that is to say, you see the circulation and respiration accelerated, convulsions supervene, and the animal dies suddenly, with an outcry.

Vallin, who has studied experimentally the phenomena of insolation, has divided into three periods the characteristic symptoms. In the first there is acceleration of the circulation and respiration; in the second period the respiration becomes retarded and sighing, and there is prostration; the third period is characterized by convulsions, coma, and death.

The post-mortem appearances in animals which have thus succumbed to artificial augmentation of heat are characterized by the early supervention of cadaveric rigidity, by the loss of electric excitability on the part of the muscles of the economy, and, lastly, by the black and tarry aspect of the blood, which loses almost all its oxygen.

Such are the results of experimentation. Are they completely applicable to the human subject? I do not think so. There is in fact a very great difference between the fever patient whose temperature is augmented by the acceleration of the combustions of the economy and the animal whose temperature has been raised artificially. Recall to mind what I said to you in a recent lecture *à propos* of the theories of fever relative to the regulation of the temperature.

Liebermeister has well shown that the very essence of the febrile process is the regulation of the temperature of the body by a standard more elevated than the normal; nothing like this takes places in experimentation on animals, and as our colleague Peter lately very cleverly said, Claude Bernard in his celebrated experiment on pigeons* performed a cooking experiment rather than one in experimental physiology, since he really heated his pigeon up to the roasting-point. It will not do, then, I repeat, to deduce from these experiments conclusions applicable to the febrile process, and they ought to be exclusively applied to the explanation of insolation, *coup de soleil.*

You see, then, that if hyperthermia is a grave symptom in the course of febrile affections, it would be a mistake to believe that in bringing back the temperature to the normal, you cause all the untoward symptoms to disappear. Nevertheless, this hyperthermia ought to engage your attention like all the other symptoms accompanying the febrile process, and just as we endeavor to raise the state of the general forces, it is our duty, when the temperature overpasses a certain level, to bring it down to a lower figure; and taken in this acceptation, the antithermic medication ought to find a place by the side of calmative and tonic modes of treatment which we employ in the clinical management of pyrexias.

* Claude Bernard, La Chaleur Animale, Paris, 1874.

Within certain limits the divers fevers respond differently to the different antithermic medicaments, and this is one of the most interesting points in the history of antipyretic medication, insomuch that of four individuals having a temperature up to 40° C., and who, if you were to judge by the sole inspection of the temperature, were having the same kind of fever, but one of whom is affected with intermittent fever, another with acute rheumatism, the third with the hectic fever of tuberculosis, the fourth with typhoid fever, none of these patients would experience just the same effects from the same antithermic medicines. In the case of the first, it is sulphate of quinine which would act the most effectively; in that of the second, it is salicylate of sodium which should be employed; in that of the third, antipyrin in small doses will give the best results (such doses, for instance, as 7 to 15 grains a day), while, on the other hand, these small doses will be insufficient to reduce the temperature in our fourth patient affected with typhoid fever, and to bring down the pyrexia in this patient, we shall have to give much larger doses. This is a very important point, on which I cannot too much insist, and which shows the specialization of the different antithermics whose history I have traced.

As for antipyrin, its elective action is seen particularly in the fever of tuberculosis, and we have here a result which is very remarkable, for up to the time of the discovery of this medicament we were

almost impotent against this hectic fever. Sulphate of quinine, even in doses of 12 to 15 grains, scarcely reduces this fever, while producing phenomena of cerebral excitation, and this is why Jaccoud proposed to substitute it for salicylic acid. The disadvantages of the latter medicine are considerable, for in large doses it produces, like quinine, vertigo and cerebral complications, while in small doses its effect is almost *nil*.

Antipyrin moreover, when given in the doses indicated by Filehne, namely, 75 grains in three doses—30 grains at first, then two hours after, 30 grains, then after two hours 15 grains — has the inconvenience of determining profuse sweats which exhaust the patient. But now that we employ the method laid down by Huchard, namely, to give only 8 grains every day, or every two days, we derive from this medication a real benefit. The patient does not experience that poignant heat of the skin which characterizes the larger doses, his sleep is better, his sweats are lessened, and the antithermic medication coupled with superalimentation, and with medicaments which modify the expectoration, enables the patient to live longer and to struggle to some advantage against his disease, even if the case be incurable.

Daremberg nevertheless employs a different method in the administration of antipyrin. He gives it especially in the apyretic period, and he exhibits it not to combat a febrile paroxysm already existing,

but to prevent one from coming on. He administers as much as 90 grains of antipyrin a day in fractional doses of 15 grains. He affirms that by this means he not only absolutely arrests the fever, but also avoids the depressant and sudorific effect of the medicine.*

Antipyrin is also applicable in those ephemeral fevers, often so intense, which accompany amygdalitis, or quinsy. You are all familiar with this febrile state, which is sometimes so grave and alarming. The skin is burning hot, and the temperature sometimes exceeds 40° C. There is agitation and even delirium, and as local signs you notice nothing but a little redness in the fauces. Here also antipyrin will give you good results. It brings down the temperature, and by the perspiration which it produces, it alleviates the dryness of the skin.

In pneumonia you can also make use of antipyrin when the temperature becomes too high. In fine, among the eruptive fevers I will mention scarlet fever as a disease where the powerful antithermic action of this medicament will find its indications in the anomalous and hyperpyrexial forms.

As for quinine, it will remain the antithermic medicament *par excellence* of morbid periodicity; for despite the action so marked and powerful of the new antithermics, they seem to have only an uncertain

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* Daremberg, on Antipyrine in the Fever of tuberculosis. (Bull. de Ther., July 30, 1885).

effect in intermittent fever. There have, indeed, been several trials made of late with resorcin and quinolin, but notwithstanding the favorable results obtained, especially with the latter medicament, quinine still remains the most powerful remedy against fever and ague.

As for the fevers of rheumatic nature, it is salicylic acid, or rather salicylate of sodium, which you should employ. Here the medicament has not only an antithermic action, but also an analgesic action of the most marked kind, and constitutes a real specific medication in acute articular rheumatism. Bernheim of Nancy has indeed maintained that antipyrin gives the same results as the salicylic medication in acute articular rheumatism, but the few trials which we have made in our hospital with antipyrin in rheumatism have not confirmed the statements of the professor of Nancy; and while we have obtained quite favorable results from this remedy, they are nevertheless inferior to those obtained from salicylate of sodium.

Perhaps we should make an exception in the case of rheumatism of hyperpyretical type, or cerebral rheumatism, where possibly thallin, which proves so powerful in small doses, may be indicated. As for typhoid fever, I recognize the fact that the new antithermics, while enabling us to bring back the temperature to the normal, do not modify the march of the disease, and in very many cases where we have employed antipyrin in the treatment of typhoid fever

we have indeed depressed the temperature, but as soon as we left off the administration of the medicament the hyperthermia reappeared with a new intensity, and the grave forms continued grave.

For my part, till something better is found, I prefer baths in typhoid fever to all these medicaments. I do not, indeed, mean cold baths, after the method of Brandt, but tepid baths. I have for more than ten years extolled the advantages of these baths over cold baths, and my opinion is every day being confirmed. I administer these baths at a temperature of between 35° to 36° C. (95° to 97° F.), so that there shall be at least three degrees of difference between the temperature of the patient and that of the bath, and I prolong the bath half an hour, three-quarters of an hour, according to the strength of the patient, which I support by giving at the same time alcoholic stimulants and broth.

I obtain from these baths thus administered a triple effect: They keep the skin cleansed; they cause an abatement of the nervous symptoms, producing repose and calm; and they have an undoubted antithermic action.

The application of new antithermics to typhoid fever well shows that the fever is not the only enemy, and that in reducing the temperature alone you only attack the disease in one of its phases; and that if, in my opinion, the cold baths, and, better still, warm baths, are preferable, it is because their effects are

complex, and are addressed rather to the troubles of the nervous system than to the hyperthermia.

Such are the considerations which I desired to present to you respecting the antithermic medication. In the next lecture I shall show you the progress which therapeutics has made in calming and removing pain; in other words, I shall set forth the new anæsthetic and hypnotic medications.

CHAPTER XIII.

ON THE NEW HYPNOTICS.

GENTLEMEN: "It is a divine work to relieve pain," says Hippocrates; and, in accordance with this verity, the efforts of physicians have in all ages been put forth to mitigate the sufferings incident to the diseases of humanity. This is often the chief duty of the medical man as he finds himself in the presence of a fatal malady.

To-day the means for alleviating pain may be divided iuto four great groups: 1, Hypnotics, which produce sleep, and thus bring the desired repose and calm: 2, Analgesics, which are addressed principally to the element of pain: 3, Anæsthetics, which extinguish sensibility, in whole or in part: 4, In the last group are placed medicaments which diminish the excitation of the nervous system, and which have been of old described under the name of *sedatives* and *antispasmodics*.

Each of these groups has received precious additions the past few years, and I propose now to devote my attention to the study of the first, namely, the new hypnotics.

Hypnotics (from ὑπνόω, I sleep) are medicines which produce sleep; and in order that the way these substances act may be understood, I shall briefly sum up the physiological phenomena which take place during sleep.

Many theories have been put forth as to the physiology of sleep, but at the present day most physiologist are agreed that the proximate condition of sleep is a diminution in the cerebral circulation—a real transient anæmia of the brain. It is well known, since the researches of Quetelet, and especially of Milne-Edwards, whose recent loss science deplores, that the general circulation is retarded during sleep, that the number of pulsations is reduced, and that the combustions of the economy are slowed. The cerebrum participates in this diminution of the circulation, and we have a certain proof of this in the various experiments made by Hammond and Durham, according to which, in dogs whose crania had been trephined, examination of the brain during sleep revealed a considerable diminution of the intracranial circulation.

These facts were confirmed in 1877 by Salathé, who showed, in his thesis on the movements of the brain, that during sleep there is a notable lessening of the cerebral expansion—an expansion which you well know is in direct relation with the arterial irrigation of the encephalon. Finally, these facts have been verified by the remarkable experiments of Mosso. This physiologist has been able, in the case of a woman whose cranium had in part been destroyed by syphilitic necrosis, to register the expansive movements of the brain, and his researches have demonstrated these two important facts: That every intel-

lectual effort augments the circulatory activity of the brain, and that it is during sleep that these movements of expansion attain their minimum.

Hence, then, every medicament which has for its effect slowing of the cerebral circulation may become a hypnotic, while, on the contrary, medicaments which congest the encephalon cannot be ranked in this category. It is understood that in the hypothesis which I have invoked to explain sleep, the anæmia and the congestion of the cerebrum must not exceed certain limits, for when the cerebral anæmia is extreme it produces convulsive paralytic phenomena; and on the other hand, when the congestion is too intense, there supervenes a state of sopor which simulates natural sleep.

But, it may be asked, what are you going to do with opium and its alkaloids, which are known to be provocative of cerebral hyperæmia; are they not hypnotics? I reply without hesitation, that I consider opium much more an analgesic and stimulant than hypnotic. In my opinion, opium does not cause sleep, despite the *virtus dormitiva* imputed to it by the medical undergraduate in the immortal comedy of "Malade Imaginaire." I know that in affirming this view I oppose traditional beliefs, but the more I study this question of opium, the more I am disposed to maintain my opinion.

Opium and morphine taken in therapeutic doses do not determine true sleep; they produce a special

state of drowsiness, of reverie, and even of beatitude, but during which the cerebral functions, powerfully excited by the congestion determined by the opiate, continue to be active, and often in an extraordinary degree. These properties of cerebral excitation invest this drug with a powerful charm, and constitute the main motive to that modern vice described under the name of morphinomania. I appeal in this connection to all who have ever made use of opium, and it will be found that the greater number will testify that they have found in this drug not a sleep-producer, but a potent calmer, under whose influence every painful consciousness is allayed.

Two new medicaments deserve especially to be studied among the hypnotics—chloral and paraldehyd. I shall be brief respecting the first of these substances, for we are all now quite familiar with that admirable medicament which Liebreich introduced into therapeutics in 1869; to-day it is by the thousands of kilogrammes that chloral is used. I must, however, call attention to the fact that this drug is an irritant, and in 1871, during my researches with Herne, which enabled us to affirm the antiseptic properties of chloral, we had a good deal to say about the caustic action of this body. It is not, then, surprising to encounter in persons who make an abuse of chloral (for there are *chloralics* as well as *alcoholics*) gastric troubles precisely similar to those determined by the alcohols.

It is, then, always necessary to dissolve chloral in a great quantity of menstruum, and I have generally been accustomed to order this medicine in egg and milk emulsion. Despite these precautions, chloral is often badly supported; in this event, I recommend its introduction by the rectum, and have found it well tolerated when given in the form of enema, the dose of the hypnotic being rubbed up with a small cup of egg and milk. As for the administration of chloral by the hypodermic method, this mode ought to be reserved for cases of extreme urgency, such as strychnine-poisoning and puerperal convulsions, for the irritant action of these injections frequently determines eschars more or less extensive.

Many have been the hypotheses framed to explain the action of chloral; some authorities basing themselves on such experiments as those of Personne, who found chloroform in the blood of chloralized animals, have maintained that it is by being decomposed into chloroform and formic acid that chloral acts. Others, on the contrary, have asserted that it exerts its power by properties of its own, not by the products of its decomposition. I quite agree with this view, and have no doubt that it is by acting directly as *chloral* on the nervous elements of the brain and spinal cord that this drug determines its hypnotic and anæsthetic phenomena, and I invoke in support of this opinion the experiments which I performed a dozen years ago, and which I now reproduce before you.

You see before you a hare, under whose skin we will now inject a solution containing 45 grains of chloral. The animal, after uttering several outcries determined by the local caustic action of the solution, falls rapidly into a state of anæsthesia, absolutely similar to that caused by chloroform, and this condition lasts till the chloral ceases to be eliminated by the urine unchanged. How are we to explain the speedy total anæsthesia of this animal, if the theory of the breaking up of the chloral into formic acid and chloroform is adopted, a decomposition which requires a long time for its accomplishment, and which produces so feeble a liberation of chloroform that anything like profound anæsthesia would be impossible with such doses? But, while acting in the form of unchanged chloral on the nervous elements, this substance has the same action as chloroform—that is to say, it produces anæmia of the brain. In this regard the experiments of Hammond are absolutely demonstrative. Chloral, then, must be classed among the true hypnotics – that is to say, among the medications which produce sleep by anæmiating the cerebro-spinal axis.

But by the side of these hypnotic properties it will not do to forget that chloral has an action on the heart, and, as Gubler has said, it is a cardiac poison in large doses, and in chloralized animals the heart is found in diastole. These three chief effects of chloral; its property of decongesting the cerebro-spinal

axis, which renders it hypnotic, its action on the heart, and, lastly, its irritant effects on the stomach, ought to serve as our guide in the therapeutic application of this admirable medicament. In all the pyrexias of congestive form chloral will prove itself superior to opium as a sleep-producer; also in typhoid fever, in pneumonia, in alcoholic delirium, it is to chloral that we should resort to calm the agitation of our patients. In cases of rebellious insomnia in neuropathic patients, chloral is the hypnotic to choose. On the other hand, chloral should be interdicted to persons suffering from cardiac affections, and in particular to those that have aortic stenosis or insufficiency; here opium is far superior. We should also refrain from prescribing chloral for patients affected with stomach disorders, for its irritant local action singularly aggravates the dyspepsias, especially those of irritative form. Finally, in diseases of the larynx and pharynx, the administration of chloral by the mouth becomes very difficult, by reason of the sensation of burning in the back of the throat which attends the swallowing of the potion. But here again we can employ the enema of chloral, which is one of the best modes of introduction of this medicament.

Chloral, again, proves a good medicament in certain forms of poisoning, especially in strychnine-poisoning, delirium tremens, and the uræmic poisoning of eclamptic form. In all these maladies it gives good results, but inferior, nevertheless, to those ob-

tained by paraldehyd, of which I am now going to speak.

The aldehydes, taken in their aggregate, constitute to-day a special group of considerable size, to the study of which my colleague and friend, Dr. Bourgoin, has devoted an entire volume.* They are, as we all know, dehydrogenated alcohols, or, better still, the hydrides of alcoholic acid radicals. We shall here occupy ourselves only with ethylaldehyd, or, as it has been called, acetic aldehyd, or, better still, hydride of acetyl, having for its formula C_2H_4O, the formula of ethyl alcohol being C_2H_6O.

Paraldehyd is a body which is constituted by the union of three atoms of aldehyd, and has for its formula $C_6H_{12}O_3$, or, preferably, 3 (C_2H_4O). Paraldehyd, when kept at a temperature of 10° C., is a solid crystalline body, which melts above the temperature just given. This fusion-point enables us to distinguish the pure paraldehydes from those that are not pure. In commerce two kinds of paraldehydes are to be found—the one liquid at 0°, the other solid at 10° C. It is to this last alone that the name of pure paraldehyd belongs.* This paraldehyd pure, is soluble in alcohol and in water; ten parts of water dissolve one part of paraldehyd, and this degree of solubility enables us to formulate the different preparations of which I am going to speak, and among which I shall

* Bourgoin, Des Aldehydes (Encyclop. Chemique, 1885).

signalize here especially two formulas which have been proposed by Yvon, the one a potion, the other an elixir. The potion is as follows:

Paraldehyd, 2 grammes (ʒ ss);
Linden [or camphor] water, 70 grammes (℥ ii and ʒ iiss);
Tincture of vanilla, gtt. xx;
Syrup of wild cherry, 30 grammes (℥ i).
M.

The formula of the elixir is as follows:

Paraldehyd, 10 grammes (ʒ iiss);
Alcohol at 90°, 48 grammes (℥ i and ʒ ivss);
Tincture of vanilla, 2 grammes (ʒ ss);
Water, 30 grammes (℥ i);
Simple syrup, 60 grammes (℥ ii).
M.

A tablespoonful of this elixir contains one gramme (15 grains) of paraldehyd. The potion may be given in the same dose. In my own practice I generally use the following formula, which is the same as that of solutions of iodide and bromide of potassium:

Paraldehyd 15 parts (or ʒ iij).
Water, 350 parts (or ℥ vi).

Each tablespoonful contains one gramme of paraldehyd, and I give the solution with some kind of liquor—rum, whiskey, or kirsch. Paraldehyd has a quite special disagreeable odor, which resembles the smell of a tippler's breath; and it is by mixing it

* Yvon.

with alcoholic liquors of pronounced taste (like kirsch or rum) that you best get rid of this taste and odor. Dr. Desnos makes use of mucilage of gum sweetened with gooseberry syrup for vehicle.

Paraldehyd has also been given in the form of enema, especially in insane asylums, and Kéraval and Nerkam have employed the following formula:

℞ Paraldehyd, 2 grammes (ʒ ss);
Yelk of one egg;
Infusion of marshmallows, 120 grammes (ʒ iv)
M.

These physicians claim that enemata of paraldehyd are superior to enemata of chloral, and according to them the active dose by enema would appear to be one-half less than by mouth. These same practitioners have employed paraldehyd in subcutaneous injections (always in insane patients). Their formula is as follows:

℞ Paraldehyd, 1 part;
Cherry-laurel water, 1 part;
Distilled water, 3 parts.
M.

Each gramme of this solution represents 20 centigrammes (3 grains) of paraldehyd. These injections, according to their statement, have always been safe, though very painful. The experiments which I have made with paraldehyd in subcutaneous injections have almost always determined in my patients not only pain, but inflammatory indura-

tions, and even abscesses. I think, therefore, that we ought absolutely to banish from therapeutics subcutaneous injections of paraldehyd.

In what dose should paraldehyd be administered? Ordinarily we may obtain the desired effect by giving from two to three grammes, and this in one dose. But, before going further, it is necessary to know the physiological action of this substance.

In 1878, in our experimental researches undertaken to ascertain the toxic power of the alcohols (I allude to the labors of Audigé and myself), we took care not to omit the aldehydes; and resuming the experiments already made by Lussana and Albertoni in 1874, we showed that in the dog we could cause death with extreme rapidity when we introduced under the skin of this animal from 1.60 gramme to 2 grammes of paraldehyd per kilogramme of the weight of the body, and that in less doses we produced a very speedy and profound intoxication; and therefore we have assigned to paraldehyd an important part in the poisoning produced by badly rectified or impure alcohols, which contain always notable quantities of this substance.

Since the introduction of paraldehyd I have desired to take up anew this study, and see if any useful therapeutic applications could be derived from it. Acetic aldehyd cannot be employed of itself. This substance is so volatile that when you introduce a teaspoonful of it into the mouth it immediately be-

comes vaporized and cannot be swallowed. I then undertook to employ a solid and stable combination of aldehyd, the aldehydate of ammonia, a crystalline and perfectly soluble body; but the aldehydate of ammonia is irritant and caustic, and when injected under the skin or introduced by the mouth it produces by its causticity such disorders that it cannot be employed.

Paraldehyd was introduced into therapeutics by Cervello in 1883; then appeared successively the labors of Albertoni and of Morselli in Italy, of Gugl and of Peretti in Germany, of Masius in Belgium, and, finally, my own studies in this country; and you will find in the remarkable thesis of my pupil, Dr. Coudray, defended April 25, 1884, the principal conclusions at which we arrived. Still more recently our colleague and friend, Dr. Desnos, has communicated to the Academy of Medicine the results of his experiments.*

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*Cervello, Paraldeide come antagonista della Stricnina (Arch. per le Scienze Mediche, t. vii. 6); Ueber die physiologische Wirkung des Paraldehyds und Beitrag zu den studien ueber das Cnloralhydrat (Arch. f. experim. Pathol. und Phar. macologie, t. xvi. cah. 3 et 4); Sull'aziohe fisiologieca della Paraldeide contributo allo studio del Cloralio idrato (Arch. per le Scienze mediche, t. vi., No. 12). Albertoni, Archives italiennes de biologie, t. iii, fasc. 2. Morselli, Irrenfreund, t, xxvi. 3, 1883. Bergesio, Rivista sperimentale di freniatria e di medicina legale 3e fascicule, 1882. Peretti, Ueber die schlafmachende Wirkung des Paraldehyds (Berl. Klin. Woch-

We experimented with paraldehyd on different animals—frogs, hares, guinea-pigs, and dogs—introducing the toxic agent under the skin. When in the dog the dose of 2 grammes per kilogramme is attained, death is rapidly caused, with complete anæsthesia and loss of all the reflexes; and if the phenomena which manifests themselves are attentively observed, it will be seen that paraldehyd affects successively the cerebrum, the spinal cord, and the bulbus. This loss of the reflexes produces a double action on the circulation and on the respiration; there is a retardation in movements of the heart and diminution in the arterial tension, as well as in the respiratory movements. Paraldehyd, then, produces effects similar to chloral and chloroform, which cause sleep and anæsthesia by anæmiating the cerebro-spinal axis. It is, then, a hypnotic in the true sense of the word. The sleep determined by paraldehyd is very like that produced by chloral; it is generally calm, but in many cases it is preceded by a period of excitation or agitation resembling alcoholic intoxication.

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enschrift, No. 40, 1883). Gugl, Ueber Paraldehyds als schlafmittel (Zeitschrift f. Therapie, 1883, 1er août) Berger, Breslauer ærtzl. Zeitschr., t. v. 6, 1883. John Brown, On the Therapeutic and Hypnotic Employment of Paraldehyd (Brit. Med. Journ., May 19, p. 956, 1883). Langreuter, Arch. f. Psych. Nervenkrankheiten, xv. fasc. 1. Coudray, De la paraldéhyd (Thèse de Paris, 1884). Desnos, De la paraldéoyd (Bull. de thér., t. cix., 1885, p. 52).

To return to the physiological action. Despite the affirmation of Quinquaud and of Henocque, who have maintained that paraldehyd acts on the hæmoglobin, causing the production of methæmoglobin, the experiments of Hayem tend to show that this view is erroneous, and that paraldehyd has little or no action on the coloring principle of the blood-globules.

But there is one point pertaining to these physiological studies which is exceedingly interesting, and which has been put in clear light by the Italian experimentors, and confirmed by the experiments of Coudray. I refer to the antagonism which exists between strychnine and paraldehyd. The experiment which I am going to peform before you will enable you to understand this antagonism.

You see before you two hares. In one of them we inject 2 grammes of paraldehyd into the cellular tissue, the other receives none. A little strychnine is now introduced in the same way. The hare is extremely sensitive to this poison, and 1-300 of a grain is sufficient to cause death. Under the skin of the hare which has received no paraldehyd 1-60 grain of strychnine is now injected. This animal immediately falls into the tetanic convulsions which characterize this species of poisoning, and shortly succumbs. In the hare that was dosed with paraldehyd, 1-12 of a grain is now injected (we may even go so far as one-tenth without causing death). You see that no serious results follow, proving that the hare that is

treated with paraldehyd will bear doses thirty times larger than the fatal toxic dose. It is the same with the dog; an animal of middling size will succumb when you administer to it 1-30 of a grain of strychnine. When it is under the influence of paraldehyd you may give it 1-6 of a grain without producing death. How are we to explain this antagonism?

This question deserves a brief consideration. We can give a physiological explanation, based on a curious experiment of Claude Bernard and Paul Thenard. They etherized hares, then injected anhydrous Prussic acid under the skin. Whenever the animal was plunged into the anæsthetic sleep they could give him quite large doses of Prussic acid without producing poisoning; but toxic symptoms appeared as soon as the animal recovered consciousness and sensibility.* The experiment to which I have just alluded may be tried with chloral or chloroform, and we shall see that the results are the same as with paraldehyd.

We may even go farther, and affirm that between alcohol and strychnine there is the same antagonism; and the experiments of Amagat, of Luton, and of Jaillet have proved that if by strychnine one may prevent the grave accidents of acute alcoholism from being produced, conversely the phenomena of strychnine poisoning may be prevented by giving sufficient doses of alcohol.

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* Dujardin-Beaumetz, "Clinical Therapeutics," p. 15 (published by Geo. S. Davis, 1885.)

Physiological researches have shown that all these medicaments—chloroform, ether, chloral, alcohòl—act directly, unchanged, on the nerve-cell; and in some of my experiments I have indubitably shown, both in men and animals, the presence of undecomposed alcohol in the cerebral substance. We know, also, that strychnine has a marked action on the central elements of the cerebro-spinal axis; so that one may say that when a nervous element is impregnated by a medicament, it refuses, within a certain limit, to receive the impression of another medicament; and it is thus that we can explain in a physiological and scientific manner the antagonism which exists between the different substances which I have just enumerated and strychnine.

But it seems to me that we may go further, and explain the tolerance and intolerance of a certain number of medicinal substances. Medicines which have an elective action on the nervous system ought, in order to produce their effects, to act on the nervous elements in a perfectly healthy state; and it is sufficient there shall have been cellular impregnation by another medicament, or a molecular modification, however inappreciable, in order that the natural effect of a drug shall not be felt; and it is in this way, in my opinion, that we are to explain the astonishing tolerance which certain inebriates manifest to substances of the most toxic nature. It is for this reason that in delirium tremens one may give immense doses

of opium, or of strychnine, etc., without dangerous results. Likewise maniacal patients, for similar reasons, often show a strange tolerance for certain poisons. I will take as example the treatment of certain forms of madness by preparations of morphine. There are, in fact, cases where physicians will not hesitate to inject at once several grains of this alkaloid, and this without any bad effects.

In a similar way I would explain the tolerance and intolerance of medicines which some neuropathic patients present, and which Huchard has characterized by the happy term, *therapeutic ataxia*. We in fact see our hysterical patients suffer toxic symptoms from minute and almost homœopathic doses of certain medicaments, and bear without injury very large doses of other extremely powerful medicines. But let us return to paraldehyd, and consider the uses which may be made of this medicinal agent.

Paraldehyd, compared with chloral, has these advantages over the latter: it is less irritating, and for this reason it is better tolerated by the stomach and pharynx; it is not a cardiac poison, and, moreover, it works better than chloral in strychnine-poisoning, but it is less analgesic than chloral—that is to say, it calms pain less; therefore, whenever the insomnia is caused by pain, paraldehyd will show itself inferior to chloral, and especially to morphine. On the other hand, In nervous insomnias, and especially in those produced by the abuse of alcohol,

paraldehyd is much superior to chloral, and I have many times seen in my hospital service the great benefit which may be derived from paraldehyd in the disorders arising from inebriety.

Much use has been made of paraldehyd in the various forms of mental alienation. In France it is Dr. Kéraval and Dr. Nerkam who have made the greatest number of trials with it in maniacal diseases. They have shown that parldehyd is an excellent hypnotic in certain forms of insomnia with restlessness, and which are so common in the course of cerebral affections. They have also noted good effects in the convulsive neuroses, and in particular in the epileptic crises and multiple manifestations of hysteria.* I will add that in many cases of morphinomania I have been able to replace the morphine injections to which the patients were habituated by paraldehyd in the dose of three or four grammes a day.

It has been affirmed that chloral is superior to paraldehyd in the fact that the latter drug sooner loses its effect on patients than the former drug. My observations do not bear out this view and I have seen patients who for months have always obtained the same effects from the same doses. I might cite, for instance, the case of a Mexican affected with

* Kéraval et Nerkam, Action hypnotique et sédative de la paraldéhyd dans les différentes formes d'aliénation mentale (Soc. médico-phychol., Mai, 1884); Nerkam, Thèse de Paris, 1884.

chronic icterus, who has for more than a year been relying on a 3-gramme dose of paraldehyd to get his sleep at night, and who never has been obliged to increase the dose; and it is the only agent which we have found capable of safely combating the tormenting itching which deprives him of sleep, all other hypnotics having failed in consequence of determining ill effects on the part of the liver or stomach. I think, then, that paraldehyd does not lose its remedial power as soon as has been represented, and among the hypnotics it is one of those that may be the longest continued with the least inconvenience. Paraldehyd seems, then, to me to be especially indicated in strychnine-poisoning, and I believe it perfectly applicable to the treatment of eclampsia.

Urethan.—Urethan, as you see, presents itself under the form of white transparent crystals, having a fresh savor, resembling that of acetate of potash; it is soluble in alcohol, ether, and water. Its chemical composition is quite complex; it is considered as a carbamate of ethyl. Carbamic acid is a hypothetical acid which has not yet been isolated, and which has a resemblance to urea, whence the name urethan given to the ethyl compound, of which the chemical formula is $C_3\ HN_7\ O_2$.

Urethan was introduced into therapeutics by Schmiedeberg, of Strasburg, and it has been the subject of experimentation by von Jacksch of Vienna, Riegel of Giessen, and by Huchard and Eloy in France.

Urethan seems to be little toxic, and we may give to a hare as much as three grammes without producing any other effect than a general lethargy. In man it requires three to four grammes to obtain a hypnotic effect.

By reason of its solubility, urethan is easily administered. Huchard's potion, which is a favorite mode of administration, is as follows:

Urethan, ʒ i.
Dill water, ℥ i.
Syrup aurantii cort., ℥ ss.

M.

Sig.: One dose, for a sleeping draught.

A solution may be prepared in water, as follows:

Urethan, 1 part.
Water, 5 parts.

M.

Each teaspoonful of this solution represents 15 grains (1. gramme) of urethan.

In fourteen patients to whom Huchard gave urethan he obtained sleep in almost every instance in the dose of 45 to 60 grains, and this especially in the insomnia of the tuberculous. In the trials which I have made with urethan in Cochin, I have obtained also good effects; but these have been less constant than in Huchard's patients, and in three cases, instead of inducing sleep, I have seen severe nervousness and restlessness follow the administration of urethan. This medicine, not being toxic, may be given to in-

fants, and in a two-months old babe Huchard procured sleep with a dose of three grains.

Although we do not yet know the physiological action of carbamate of ethyl, we can affirm that it is a hypnotic, but it is not an analgesic, and when the insomnia is caused by pain it is without effect.

[SULPHONAL.—Since the first edition of this work, a new hypnotic has been discovered to which the name sulphonal has been given.

The chemical name *di-ethyl-sulphon dimethyl-methan*. The process of fabrication is very complex, and is described in the Therapeutic Gazette for 1888, page 377.

Sulphonal crystallizes in large colorless tables, and is perfectly devoid of odor and taste. It is rather insoluble in water, requiring twenty parts of boiling and one hundred parts of cold water for its solution. It is quite soluble in alcohol, not affected by strong acids, and is an extremely stable body.

Sulphonal can hardly be called toxic in ordinary doses. It is an extremely valuable hypnotic. The dose is ten to sixty grains, taken an hour or two before bedtime.

In my own practice, I have seen reasons to be much pleased with the effects of this new hypnotic. It produces sound and refreshing sleep, much more like natural sleep than the sleep of chloral, and I have seen no pleasant after-effects; not even the giddiness of which some writers have spoken. I have given it to children for insomnia due to hyper-excitability of the nervous system due to teething and other cause, and seen it work admirably. The dose for an infant in one or two grains. Five grains may be given to a five-year-old child. For adults, a ten-grain dose is sometimes sufficient to restore the normal sleep. In my own person, I have known ten grains to give six hours' sound sleep, and the sleep is so refreshing that to me sulphonal is the ideal hypnotic. It is understood that sulphonal does no good in the insomnia due to pain.

It is a pity that the drug is under the ban by being a patented medicine.—TRANS.]

CHAPTER XIV.

ON NEW ANALGESIC MEDICAMENTS.

My last lecture was devoted to medicaments which produce sleep (hypnotics); to-day I propose to speak about analgesics, that is to say, medicinal substances which antagonize pain. I shall dwell more particularly in this lecture on the new analgesics; aconitine, napelline, gelsemium and gelsemin, piscidia, and finally on the local anæsthetics such as subcutaneous injections of chloroform and pulverizations of chloride of methyl.

The type of analgesic medicaments is morphine, and if opium and its derivatives are considered as hypnotics, it is because they give repose by banishing all painful sensations. I cannot here enter into the subject of subcutaneous injections of morphine, which I have treated at length in my Clinical Therapeutics. However, the older I grow, the more chary I become in the use of morphine, for despite the marvellous properties of this alkaloid, which is far the most active of analgesics, its dangers and disadvantages are such that I reserve its employment for exceptional cases only.

In fact, the superiority of morphine constitutes one of its most serious evils. Let me explain: Whenever a patient has once made use of morphine, thereafter all other analgesics seem inefficacious and unsat-

isfactory, and he looks continually to the same medicament for the relief which he has experienced, and when the pain is entirely gone he will have become so accustomed to his morphine that he will with difficulty, if at all, free himself from the habit. This is the history of almost all cases of morphiomania; at the beginning it is for a neuralgia, a mild attack, perhaps, for which the patient has recourse to the injections of morphine, and little by little he becomes habituated to the poison, and when he is once a victim to this vice, it will be very difficult to make effectual opposition to it.

Do not, then, resort to these injections except when you have to do with intense pain caused by cancer or in the last periods of pulmonary diseases; here morphine is really advantageous, enabling us to prolong the life of these unhappy beings and make them tolerably comfortable. In all these cases never allow the patient to make the injection himself, and only resort to them when the pain becomes too severe, and not till you have employed all the other means in your power.

Aconite, after morphine, is one of the most powerful analgesics, and the subject of aconite and aconitine deserves to arrest your attention for a few moments, illustrating, as it does, how complex is the application of medical plants to medicine, and how cautious we should be in deducting positive conclusions from any

observed sequences in the therapeutic use of these agents.

For a long time, practitioners in this country made use of preparations from aconite leaves, and the results obtained were very problematical. Oulmont, in showing us that the active principles of the plant vary according to its origin and the parts used, made apparent the cause of the seeming inertness of these aconite preparations, for the leaves contain very little of the active principles, while the roots are largely impregnated with them. Hence it is that in England, where the Pharmacopœia sanctions the usage of the root alone for the officinal preparations, very energetic results have been obtained from these latter. Duquesnel, in extracting from these aconites a definite crystalline principle, added still more to our knowledge of this plant, and his studies, in connection with Laborde, of aconite and aconitine have been of great value.

There exist two great varieties of aconite, the one growing in Europe, the other in Asia; the French aconite may be subdivided into the *Aconitum anthora* and the *Aconitum pyrenaicum* with yellow flowers, the *Aconitum Napellus* with blue flowers; the type of the Asiatic aconites is the *Aconitum ferox*.

When you analyse these different plants, you find that they contain a crystalline aconitia, an insoluble amorphous aconitia, and another which is soluble, to which Duquesnel has given the name of *Napelline*. Moreover, in the Asiastic aconites, there is found an-

other crystalline alkaloid, *pseudo-aconitina*, and an amorphous alkaloid, *amorphous pseudo-aconitina*. Finally, what is still more astonishing is that, according to the origin of the aconites, these alkaloids behave differently with respect to polarized light.

You see before you two solutions of crystallized nitrate of aconitia; the one comes from the *Aconitum Napellus*, gathered in Dauphiné, and deviates the polarized ray to the left by 3°.4; the other is obtained from a plant growing in Switzerland, and is also lævogyrus, but by 4°.8.

You see how complex is this question of the aconitias, and how different must be the result according to the plant employed. There exist in commerce English and German aconitias, an aconitia of Morson, another of Duquesnel, etc., and all these aconitias have variable therapeutic and physiological actions, for the reason that they are derived from plants of different origin. It will, then, be absolutely necessary, when you wish to prescribe aconite or aconitia, to specify the part of the plant and its place of origin, if you write for aconite, and the laboratory where it was extracted if you order aconitia.

We actually make use almost exclusively of the alcoholic tincture of aconite root, and we add the name of the province, whether of Vosges or Dauphiné. Duquesnal thinks that the tincture is preferable, and he proposes the two following preparations: The tincture of aconite root, and the extract; the latter being

the most active, three to four centigrammes of the extract representing one gramme of the tincture. As for aconitia, it is the crystallized nitrate of aconitia which you should order, adding the name of Duquesnel, and under the form of granules containing a quarter of the active principle. (In American pharmacy a pill is in use containing $\frac{1}{200}$ grain crystallized aconitia.)

As for the doses, they are exceedingly variable, and you should always remember that certain persons have a real intolerance of this medicament. I have, for my part, seen toxic-phenomena of great gravity determined by extremely minute doses of crystallized aconitia, scarcely the $\frac{1}{1200}$ of a grain.

Therefore you will have care that the doses shall be wide apart when you make use of this alkaloid, and order, for instance, a granule of a quarter of a milligramme ($\frac{1}{1200}$ grain) every six hours, giving directions not to exceed four granules in the twenty-four hours. It will even be necessary to stop the medicine when the patient experiences the first toxic symptoms, such as tingling of the tip of the tongue, and that strange sensation of loss of elasticlty of the muscular orifices of the mouth, eyes, and nose, when it seems to the patient that the skin of the face is shrunken.

If you make use of the tincture or fluid extract of the root, the dangers of poisoning are less, and you can give ten or even twenty drops, three or even four times in the twenty-four hours. The dose of the

extract is one-sixth of a grain, which you can repeat once or twice during the day.

Aconite and aconitina have a very limited sphere of action, which, as far as pain is concerned, is confined almost exclusively to the trifacial nerve; its action on the other sensory nerves is much less marked.

By the side of this analgesic effect, aconite has a special action on the circulation; it is an anti-congestive vascular medicament from which you may obtain good results, especially in the pulmonary congestions accompanied with cough, of which one of the types is influenza. You know that in this affection I have been in the habit of ordering the following mixture:

Into a glass of warm milk put two tablespoonsful of syrup of tolu, a dessert-spoonful of distilled cherry-laurel water, ten drops of tincture of aconite root, and order the whole to be taken in one dose and repeated three times a day.

Aconitia, as I have told you, has a special influence on the trigeminus, abolishing conscious and painful sensibility, and acting also on the unconscious or reflex sensibility; it modifies the blood pressure, diminishing arterial tension, and lowering the temperature. These are especially the physiological effects which are utilized in therapeutics.

Aconitia has besides another effect of which I must remind you, for it has given rise to several mistakes. I refer to its action on the pupil. Adminis-

tered internally, aconitia dilates the pupil, and this explains why physicians, seeing this mydriasis, have sometimes thought that the apothecary had made a mistake, and instead of granules of aconitine had given granules of atropine; you will not then be led astray if you should see pupillary dilatation follow the use of this alkaloid.

It is in facial neuralgia that aconitia produces its maximum of therapeutic effects, and for my part, I am acquainted with few neuralgias which are not relieved by this means. When the prosopalgia presents itself under intermittent form, you will do well to associate quinine with the aconitia. You can unite in the same capsule five grains of quinine with one two-hundredth of a grain of crystallized aconitia, or having administered a capsule containing the five grains of quinine, you can give one of Duquesnel's granules, and repeat the dose every six hours until the pain has entirely disappeared.

Aconitia is not, as I have told you, the only active principle obtained from *Aconitum Napellus*. There are also found two amorphous principles, the one soluble, the other insoluble. It is to the first of these principles that Duquesnel has given the name of napelline. Thanks to its solubility, napelline may be given subcutaneously. Laborde and Daudin have experimented with napelline, and have shown that this alkaloid is much less active than crystallized aconitia, and that, moreover, instead of being purely analgesic,

this napelline possesses quite marked hypnotic properties. They have also employed this alkaloid in subcutaneous injections in the dose of five-sixths of a grain once in the twenty-four hours, and have never seen toxic symptoms follow. Hence they think that napelline, by its less intense toxic action which renders it more manageable, is a medicament which may be employed to advantage in the treatment of neuralgias.

If you wish to repeat these trials, I advise you to adopt the following method: Make subcutaneous injections of a solution of one-sixth of a grain of napelline in a cubic centimeter of water, repeat these injections three or four times in twenty-four hours. Grognot, of Milly, has employed napelline in granules of two and a half milligrammes (one twenty-fourth of a grain), and in the dose of three centigrammes (one-half grain), he cured a rebellious facial neuralgia which had resisted the action of crystallized nitrate of aconitia. But I have no more time to spend on aconite and its alkaloids, and pass to the study of gelsemium.

Gelsemium sempervirens, or Yellow jasmine, has been employed largely by the Americans. It is a climbing plant, with yellow flowers, which grows in the moist soil of Virginia and other of the Southern States. The roots and the stem are employed in medicine; of these a tincture is made, which is given in the dose of ten drops every two hours in facial neu-

ralgias, being especially remedial in dental neuralgia. Remarkable results have been claimed, notably in the intermittent forms of neuralgia.

I experimented with gelsemium several years ago (in 1877), and my pupil, Dr. Eymeri, has given in his thesis the results which we obtained.* These results were similar to those of previous experimentors who had studied the therapeutic, toxic, and physiological action of this plant. We found that gelsemium is an energetic poison, and that its toxic action is variable, according to the preparation employed, so that one tincture made with the stem may give small or unappreciable effects, while another made with the root, may have a marked toxic action in the same dose. I have myself seen a patient who experienced severe symptoms of poisoning from thirty drops of the tincture; moreover, quite a number of fatal cases have been recorded from the use of this drug, so that while recognizing the analgesic action of the preparations of gelsemium (inferior though this be to that of aconite and its alkaloids) it has seemed to me to be wisest, owing to the acknowledged uncertainty of the gelsemum preparations, to be very chary in the use of this remedy.

It has been recommended to employ, instead of gelsemium, the glucoside *Gelsemin*, discovered by Frediдge, but we know little respecting the action of

* Eymeri, on *Gelsemium sempervirens* (Thése de Paris, 1877).

this active principle, and we ought to be well established with regard to its physiological and toxic effects before giving it a place in therapeutics. Moreover, gelsemium, its glucoside and its alkaloid *Gelsemine*, produce not only paralysis of sensibility, but also of motility, and, as Rouch has well shown, gelsemium is especially a poison of the motor-nervous system. Moreover, Rouch has also pointed out in his experimental researches, as we have also done in our clinical observations, that the effects vary according to the preparation employed.

Piscidia erythrina, or Jamaica Dogwood, is of quite recent introduction into therapeutics. The first experiments made with it, by Ott*, of Philadelphia, and Nagle, in 1881, show it to be narcotic to animals: it is, however, worthy of note that in 1844, Hamilton of Plymouth pointed out the analgesic properties of piscidia, and Ford, in 1880, recommended it in neuralgias. Since the labors of Ott and of Nagle, there have been numerous trials with piscidia, and Firth, James Scott, MacGrotz, Seifert of Berlin, and Vanlair of Liège, have published observations on the therapeutic effects of this remedy.

It was Landowski, in 1883, who was the first in France to call attention to the narcotic and analgesic properties of piscidia. Huchard has utilized it in combination with *Viburnum prunifolium*, and I have

* On the Physiological Action of the Active Principle of *Piscidia erythrina* (Arch. of Med. 1881).

myself made in this hospital, and in my laboratory, a great many therapeutic and experimental researches on this subject in connection with my pupil, Dr. Legoy of Huilles.*

Piscidia erythrina is a shrub or tree of the family Leguminosæ, which grows in South America and the West India Islands. Its name comes from the brilliant color of its red flowers, and the stupifying action of its bark on fishes, an action which is very similar to that of *Cocculus Indicus*. In America, this plant is designated under the name of Jamaica dogwood. It is the bark of the root which is used exclusively, and according to the researches of my pupil Carette, there are found in this bark the following ingredients: A resin, a terbenthinate substance, starch, a salt of ammonia, and finally an alkaloid which Bruel and Tanret have extracted. But here the same difficulties have been met with as in the case of gelsemium, the alkaloid being found in roots of one source and not in those of another, and the therapeutic results being variable and uncertain in consequence.

Besides this different composition resulting from the different sources of this dogwood bark, there is another fact which obscures its physiological action. I refer to its unlike effects on warm-blooded and on

* Hamilton, Pharmaceutical Journal and Transactions, 1884; Ford, Therapeutic Gazette; Legoy, Du *Piscidia erythrina* (Bull. de thér., 1885, t. cviii, p. 72, et Thése inaug., 1884).

cold-blooded animals. While in the case of the former the physiological action, even in large doses, is almost *nil*, in the second, on the contrary, it is very marked. When piscidia is administered to a frog, there are observed convulsive movements, an exaggeration of the frequency of respiration and of the cardiac pulsations, a tetanoid state, and finally death. Piscidia seems to act almost exclusively on the gray elements of the bulbus aud medulary centre; it acts also on the ganglionic nervous system.

It is under the form of the powder, or fluid extract, or tincture, that piscidia is administered; the latter seems to us to be preferable. I would recommend the following formulæ:

℞ Fluid extract Jamaica dogwood, ʒ ss.
Syrup aurantii corticis, ℥ viii.

M.

Sig. Take a tablespoonful *pro re nata*.

The tincture may be given in doses of from 40 to 50 drops. Huchard associated piscidia with viburnum in the following manner:

Alcoholic tincture of Jamaica dogwood.
Tinct. (or fluid ext.) viburnii prunifolii, ää gtt l.

M.

To be taken for one dose *pro re nata*.

Thus far the majority of physicians who have given their attention to piscidia consider it a hypnotic. The therapeutic applications which I have made with

this drug do not permit me to share this view, and I regard it as an analgesic very similar in its action to gelsemium, causing sleep because it relieves pain.

Moreover, the first trials made by Hamilton with piscidia (in 1884) were confirmatory of this view. Hamilton was suffering from an intolerable toothache; he applied to the gums, in the vicinity of the tooth, a pledget of cotton wet in tincture of piscidia; the relief was instant and complete. He then bethought himself to apply the same remedy internally for obstinate pain; a marked anodyne effect was realized, with profound sleep. In several cases of rebellious facial and brachial neuralgia, we have seen the pain disappear as by magic under teaspoonful doses of fluid extract of Jamaica dogwood, but like gelsemium it is an untrustworthy analgesic, and this in consequence of reasons above given. So when you prescribe piscidia, you will do well to specify the Jamaica dogwood, this being the only reliable kind. The dose of the tincture is from 30 drops to fluid drachm; the American fluid extracts are much in use and are given in the same dose. Syrup is a good vehicle for administration.

I shall finish this lecture by a brief consideration of two local means which have of late been used to assauge pain: I refer to subcutaneous injections of chloroform and to the chloride of methyl spray.

Subcutaneous injections of chloroform were first prescribed by Dr. Roberts Bartholow about ten years

ago,* but their employment in France is of much more recent date. It was in 1877 that Ernest Besnier made known the good effects which he had derived from these analgesic injections, and the following year one of my pupils, Dr. Fournier, recorded in his thesis the results of the trials which I have made with the same remedy in my service at the Hôpital St. Antoine. In these experimental investigations I found that if in man the dose of chloroform injected under the skin be raised to about two and a half drachms, sleep is produced, but without anæsthesia.

I have given in elucidation of this fact an explanation which Claude Bernard had already invoked in his studies on anæsthetics. I have shown that in introducing chloroform under the skin, this medicament, before reaching the cerebro-spinal axis, where it produces its elective action, traverses the lungs, where by reason of its extreme volatility it escapes with the air of expiration, and that the quantity which remains in the blood is too insignificant to make a very powerful impression on the nervous elements of the cerebro-spinal axis; at each inspiration, however, the patient drawing back a certain quantity of air thus charged with chloroform, obtains in this way sufficient of the anæsthetic to produce sleep and an anodyne action, but not profound insensibility.†

* Roberts Bartholow, On the Deep Injections of Chloroform for the Relief of Pain. Practitioner, July, 1874.

† Clinical Therapeutics. Published by Geo. S. Davis, Detroit. Page 12.

Professor Bouchard has repeated these experiments from another point of view which had absolutely escaped me. All the animals, and particularly the hares, under whose skin he injected chloroform, succumbed with albuminuria;† the explanation of this fact has not yet been found.

Despite their undoubted analgesic action, hypodermic injections of chloroform have not found favor, and I am inclined to attribute the abandonment of them by the profession to the local inflammatory symptoms which result from these injections when carelessly or improperly made. When you desire to make use of these injections of chloroform, do not forget that it is important to make them penetrate deeply. I advise you, then, to plunge the needle of your syringe perpendicularly, its whole length, into the fleshy parts, and there throw your injection. This, moreover, is the way that we generally make our hypodermic injections at the present day; formerly it was the custom to pinch up a fold of skin and enter the needle obliquely, parallel to the fold, and introduce the solution into the cellular tissue. The former method is certainly most rapid and advantageous.

It is well understood that these subcutaneous injections of chloroform ought to be made in *loco dolenti;* for this reason their application is rather limited

† Bouchard, On Albuminuria determined by Subcutaneous Injections of Chloroform. (Acad. de Med., 1784).

through fear of eschars and abscesses. Hence it is especially in sciatica and lumbago, or even intercostal neuralgia, (in all cases, in short, where the cellular tissue permits the deep introduction of the medicament), that these injections should be practiced. The quantity ordinarily injected is one cubic centimetre, or about twenty drops, but you may go even further, and inject at short intervals as much as two or three fluid drachms.

The application of chloride of methyl is of quite recent date, and it was in 1884 that Débove made known to us the good results which he had obtained from external applications of this chemical to the treatment of neuralgia.

Chloride of methyl, which is also called muriated methylic ether, is, at the normal temperature, a colorless gas, with sweetish odor and taste; it may be liquefied by cold or by pressure. It is under pressure that it is utilized in the cases of which I am about to speak. When liquefied, methyl chloride is a colorless liquid which boils at the temperature of about 83° F. Hence it is that it evaporates immediately when brought into contact with the air, and that by this molecular change an intense cold is produced, amounting to a fall of forty degrees, or even more.

Formerly these refrigerant properties were only employed to freeze histological specimens. This easy transformation into gas of liquefied chloride of methyl, necessitates keeping this liquid in very strong recipients.

We thought first of all of using the syphon bottles, so much employed for dispensing soda water, but had to give them up, on account of the bursting under the influence of an elevated temperature. To obviate dangers of this kind, we have had to resort to flask-shaped metallic reservoirs, which are rather complicated and costly, and this is, it must be confessed, one of the circumstances militating against the general use of this remedy. Nevertheless, now that you can hire these bottles at a reasonable cost, everybody may now avail himself of the benefits of this treatment, as the most of our instrument makers, and even the pharmacists, have this apparatus to let.*

The apparatus which I here show you (see Fig. 7) was made by Galante, and it is one on which you can rely. It consists, of a metallic bottle, which at its superior extremity has two openings closed by screw caps. By means of the wrench C you remove the screw cap B, and replace it by another screw cap E, to which is fixed a metallic tube terminated by a filiform opening, by which the chloride of methyl escapes. Then, still with the same wrench, you remove the screw cap A, and place the central part of the wrench upon a metallic nut situated at M, which holds the wrench horizontally, and it will be sufficient to turn a little, by means of this wrench, the screw faucet with which

* Unfortunately this apparatus, which is expensive, has not yet been introduced into this country. See H. B. Millard's article in the Therapeutic Gazette, February, 1885.—Trans.

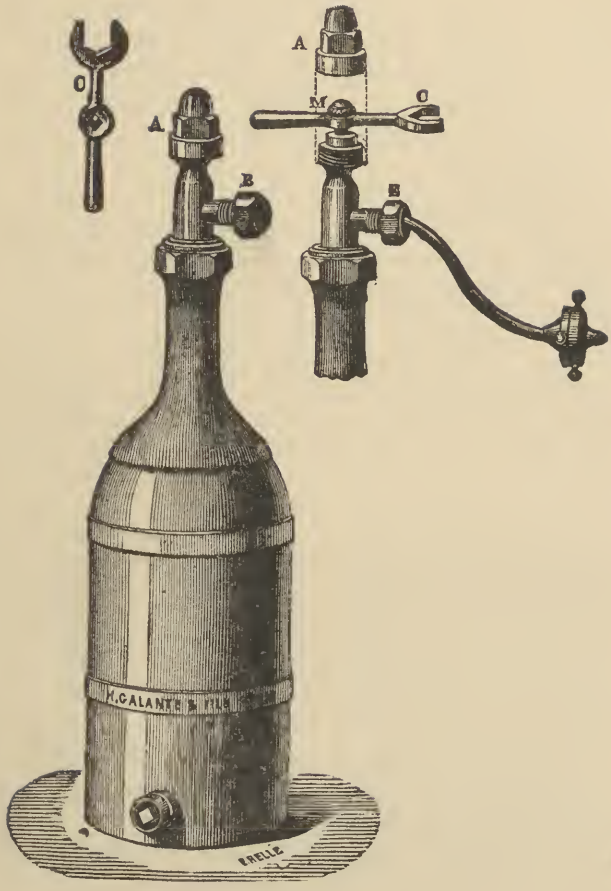

FIG. 7.

it is connected, to cause the chloride of methyl to escape by the filiform opening which I have pointed out to you. The management of the instrument is then very easy, and all you will have to do will be to pass for a few seconds over the painful points the chloride of methyl spray.

The surface of the skin which is thus touched by the methyl chloride spray becomes congealed, pale and hard, and the patient experiences a sensation of smarting and burning provoked by the intense cold which is produced. If the topical effect is too prolonged, a local mortification ensues, which consists in simple vesication or in veritable eschars. Ordinarily, and when the action of cold has been of short duration, the skin turns red, and then it assumes on the following days a brownish tint which it may keep for some time. Hence I cannot too strongly urge you not to prolong the action of the chloride of methyl, and never to let the spraying exceed four or five seconds on the same part of the skin, for the production of vesication and of eschars adds nothing to the therapeutic effect which one desires to attain. When you wish to apply the spray over hairy regions, you must first shave the skin.

The therapeutic action of these pulverizations of methyl chloride is exceedingly interesting, and if we may judge by the facts reported by Débove, and other of our hospital colleagues, and in particular by Dr. Tenneson, brilliant cures in ob-

stinate neuralgias have resulted from this treatment. You may also have seen in our hospital service the great benefits which we are deriving from this method, and when, in rebellious sciaticas, our vesicatories and punctiform cauterizations fail to relieve, we resort to the methyl chloride spray. If it be a case of real sciatica, the pain generally ceases after one or two applications of chloride of methyl. It is not so when we have to do with sciatic pains resulting from affections of the spinal cord, or compression of the nerves; here the method generally fails; yet in certain cases of sympathetic neuralgia (determined, for instance, by cancer of the womb) Desnos has had success.

Clinicians have even gone farther, and have applied the methyl chloride to the relief of the phenomenon pain, from whatever source arising; in this way Tenneson has caused to disappear the pains in the side attending acute or chronic pulmonary affections. I think that this is extending the analgesic action of chloride of methyl farther than we are warranted in doing, and that it will be better to reserve it for very rebellious neuralgias. The therapeutic application, then, of chloride of methyl spray is one of the really useful discoveries of the day, and you will do well always to resort to this treatment (which is in itself not at all dangerous) whenever you have to deal with stubborn neuralgia.

CHAPTER XV.

ON LOCAL ANÆSTHETICS.

GENTLEMEN: In the present lecture I propose to consider the new anæsthetics, and omitting altogether surgical anæsthesia in its various bearings and uses, which would require a whole course of lectures, I shall take up only one of the minor aspects of the question, and discuss the subject of local anæsthesia, which presents no little interest at the present day.

For a long time clinicians have sought to diminish or abolish the sensibility of the skin in regions where the minor surgical operations, such as simple incisions of the skin and cellular tissue, were to be performed. This was considered the more desirable, inasmuch as grave accidents sometimes attended the first attempts at general anæsthesia. One of the means most employed was cold.

It was, in fact, known that when cold strikes the exposed parts of the body it produces numbness and insensibility, and practitioners had recourse not only to local applications of ice, but also to refrigerant mixtures. Hence it is that James Arnott, of Brighton, many years ago, advised the combination of ice and common salt, and Adolph Richard, that of sal-ammoniac, salt and ice.

One may also obtain this local anæsthesia by the rapid evaporation of volatile substances, such as ether,

and Simpson was one of the first to counsel this mode of refrigeration. I remember to have seen, thirty years ago, at the commencement of my medical studies, a very ingenious apparatus made according to the plan of Prof. Richet, which consisted of a pair of bellows over which was placed a reservoir of ether; as fast as the stream of ether was projected on the exposed surface of the skin, it was volatilized by the blast from the bellows. This apparatus which was rather cumbersome, was advantageously replaced by Richardson's spray producer, of which we make use at the present day.

The atomization of ether as a process of local anæsthesia possesses great advantages over the local application of ice or refrigerant mixtures; nevertheless, these sprays are not free from the other inconveniences of refrigeration. Cold does, in fact, abolish sensibility, but during the application the pain is quite keen, and when the anæsthesia has disappeared, the pain returns more pungent than before, so that if one suffers but little during the operation, the after effect is quite painful; moreover, the reaction is sometimes followed by profuse hæmorrhage. These are disadvantages which limit the usefulness of local anæsthesia by cold.

Other liquid substances have been substituted for ether, such as rhigolen by Bigelow of Boston, and Delcomenete of Nancy a few years ago, advised carbon bisulphide as a means of local anæsthesia. I have

myself been much interested in this subject of the local uses of bisulphide of carbon. This chemical, by reason of its extreme volatility, produces refrigeration of the tissues, but this refrigeration is rapidly followed by such intense rubefaction that carbon bisulphide ought rather to be considered a rubefacient of the first order, superior in many respects to mustard sinapisms, than as a local anæsthetic. It has also been proposed to employ certain gases for the production of local anæsthesia, and it is for this purpose that carbonic acid was recommended as early as 1772 by Percival. In 1856 Simpson again took up this means of local anæsthesia, improving the apparatus for its production, and it was then quite a common thing to see local douches of carbonic acid used in the hospitals of Paris, though rather for analgesic than for anæsthetic purposes; they were used chiefly to relieve the pains caused by cancer of the uterus. We have even seen this gas employed in the treatment of neuralgias at the thermal stations, where are found waters highly charged with carbonic acid, as at St. Nectaire. Finally, in 1883, my friend Dr. Campardon, following the ancient practice of Percival and Simpson, applied carbonic acid to the treatment of whooping-cough.

Thanks to the anæsthetic properties of carbonic acid, it abolishes the exaggerated sensibility of the glottis, and thereby lessens the fits of coughing in pertussoid patients. The means employed by Campardon is very simple; it consists in utilizing

the well known soda-water syphon bottles—the bottles which are in use for this purpose are destitute of tubes dipping into the liquid, and only the liberated gas issues from the mouth of the bottle. A rubber tube adapted to the syphon, and which the patient takes between his lips, conveys the gas into his mouth; the child makes a few inspirations, and Dr. Campardon affirms that by this means he has seen the paroxysms rapidly diminished. But I come now to a mode of local anæsthesia of much more recent date, and which is destined to render us great service; I refer to coca and cocaine.

From time immemorial the Peruvians have made use of the leaves of a shrub belonging to a family of Erythroxylaceæ, the *Erythroxylon coca.* In their estimation this leaf has multiple remedial properties, and, according to the statement of Dr. Beugnier-Corbeau, "the sacred plant of the Incas was a promise of life to the moribund who could drink its sap; an incomparable viaticum to the traveler whose hunger it appeased; a cordial to raise the forces and revive the senses benumbed by the cold of the rugged winter; a source of sweet forgetfulness to the man harassed by chagrin; and a joy-producer to him who would taste the pleasures of love."

When, twenty years ago or a little more, it was proposed to introduce coca into therapeutics, it was chiefly its tonic and excitant properties which were vaunted; and you will find in the thesis of Damarle,

and in the writings of Reis, indications relative only to these tonic properties.* However, in 1860, Niemann had discovered in the leaves of coca a crystalline alkaloid having for its formula $C_{17}H_{21}NO_4$, to which he gave the name of cocaine; and, two years afterwards, Wolher and Lossen found another supposed principle, of syrupy consistence, having a very marked ammoniacal odor, to which they gave the name *Hygrine*.

These chemical discoveries added nothing to our knowledge of coca till Koller made known, on the 16th of October, 1884, to the Medical Society of Vienna, the marvellous anæsthetic action of cocaine on the mucous membrane of the eye. You remember how great was the astonishment, and what incredulity was manifested; but soon the facts which Koller had announced were confirmed all over Europe. Abadie and Darier, Trousseau, Panas, and all the ophthalmologists showed the great advantages which might be obtained in ocular therapeutics from the discovery of Koller, and the anæsthetic properties of cocaine were henceforth everywhere recognized. By what train of ideas was Koller led to make this grand discovery, which constitutes an epoch in the therapeutic history of this country? And how is it that coca, from being the tonic and waste-restraining medicament which it once was, has been transformed into a local

* Damarie, on Coca, Thèse du ductorat, 1862. Reis, on the Use of Coca, Bull. de Thér., 1866.

anæsthetic? The history is so strange that you will allow me to briefly to relate the points of interest.

Moreno y Maiz,* in his thesis of 1868, on cocaine, made mention of the following fact: "In large doses, cocaine produces in animals diminution, then annihilation of sensibility, without motility being completely abolished; in all cases the pupil remains dilated."

In 1870, Gazeaux gave expression to certain doubts respecting the tonic and waste-restraining properties of coca, and thought that this medicament might act by allaying the sense of hunger and thirst through its anæsthetic effect on the lingual and gastric mucous membranes.

In fact, physicians who were engaged in treating affections of the larynx had noticed this special anæsthetic action of coca; and Fauvel, since 1869, was in the habit of using coca in laryngeal diseases.

In 1877, Saglia insisted anew on the advantages to be derived from the sacred plant of Peru in painful affections of the pharynx, and this anæsthetic action was so well shown that, in 1881, Du Cazal,† at the Medical Society of the Hospitals, thus expressed himself *à propos* of a case of tuberculous ulceration of the larynx presented by our colleague, Millard: "The tincture of coca is an excellent medicament with which

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* Moreno y Maiz, on Cocaine, Thèse de Paris, 1868.

† Saglia, on Coca: its Therapeutic Applications, Gaz. des Hôpitaux, May, 1887. Du Cazal, Compt. Rend. de la Soc., 1881, p. 283.

to obtain anæsthesia of the pharynx, and to produce such anæsthesia it is only necessary to paint the mucous membrane with the tincture." Gougenheim,* in 1882, when writing of the local treatment of laryngitis, said: "The extract of coca, diluted in water so as to form a very concentrated solution, produces a veritable sedation; I do not know the cause of this therapeutic action."

Moreover, the physiologists on their part did not remain inactive, and, in 1880, Von Anrep spoke of the pupillary dilatation, but had not observed the state of the mucous membranes. The following year, Coupard and Laborde noticed the anæsthetic action of cocaine. Unfortunately their experiments remain incomplete, and the results have not yet been published.

Hence, as you see, what led Koller to his discovery was the knowledge of the local anæsthetic properties of coca on the lingual and pharyngeal mucous membrane; he thought, and rightly, that all the mucous membranes must respond alike to the action of this medicament; and since then we have been able to add that even the skin submits in some degree to this action.

When you put in contact with a mucous surface a two-per-cent. solution of hydrochlorate of cocaine, you obtain, at the end of from five to ten minutes, loss

*Gougenheim, on Local Treatment of the Laryngites, Soc. de Thér., 1882.

of sensibility of the mucous membrane, and this effect lasts an hour or two. The anæsthetic action does not seem to exhaust itself by habit—that is to say, a second and third, or any future application is as successful as the first. The same insensibility is produced when the cocaine is introduced under the skin, and in the experiments made upon one Christian, by Dr. Paul Compain, and which you will find described in his inaugural thesis,* I studied thoroughly the anæsthetic action of hypodermic injections of this alkaloid.

You see before you a patient on whom we are about to experiment; we pinch up a fold of the skin of the forearm and inject twenty drops of a two per-cent. cocaine solution. This injection, as you may see, does not cause any painful sensation. If in the course of five minutes, we explore the sensibility of the skin over the point of injection, this is what we shall oberve: The sense of touch is obtunded, and the patient tells us that he feels as if the skin over that place were covered with a thick layer of wadding. The consciousness of painful impressions is abolished, and we may with impunity scrach or prick the part with a needle; the patient has over this region only the sensation of contact of a foreign body. The anæsthetic state of the skin is produced in only a very limited zone, which exactly corresponds with the portions of the derm which have been directly in contact with the

* Paul Compain, Contribution to the study of hypodermic injections of hydrochlorate of cocaine, Thèse de Paris, 1885.

solution of cocaine, and in our patient it represents a circular space of abont an inch and a half in diameter. This complete anæsthesia of the skin lasts about twenty minutes, then disappears little by little, and an hour after there remains but a trace of the anæsthetic phenomena.

May these hypodermic injections be accompanied by general symptoms? Yes, in certain cases. In the first researches which were made in our laboratory by Drs. Bardet and Meyer, these experimentors affirmed that they had felt such general effects as, first, a marked dilatation of the pupil coming on half an hour after the injection, then syncopal symptoms, so intense that one of them completely lost consciousness and fell on the floor—his face was pale and his pulse impreceptible; these symptoms returned whenever he assumed the erect posture.

Since then we have observed the same symptoms in a number of our patients. One of these was a woman on whom we wished to practice forcible dilatation of the anus; we injected around the margin of the orifice a syringeful of a two per cent. solution; there supervened syncope, nausea, and curious twitchings of the alæ nasi.

I was recently consultant in a case in which I had ordered subcutaneous injections of cocaine to combat a vehement intercostal neuralgia. The attending physician wished to experiment on himself with the same injection, after having administered it to the

patient; in both there were very pronounced symptoms. The physician experienced an attack of syncope, while the patient had very strange sensations; he felt, he said, extraordinarily light, and seemed to himself to be lifted up into the air like a balloon.

In these cases the injections were practiced with a two per cent. solution, and the dose did not exceed from one to two centimetres; I must add, that in all these instances the patients were standing or sitting, which postures would be likely to favor syncopal attacks; hence it is that, since I have taken the precaution to make the patient lie down whenever I have administered the cocaine injection, these phenomena have not occurred.

To what causes must we ascribe these effects? Probably to the cerebral anæmia produced by the action of cocaine upon the vaso-motor nerves; in fact, besides the considerable part which the dorsal position plays in the appearance or non-appearance of the general effects of cocaine, it is noteworthy that these general symptoms are the more likely to supervene, the more anæmic the patient is, and that they are inconspicuous when the patient is strong and vigorous. Hence it is that Dr. Compain has never seen such accidents produced as the results of numerous injections which he has made on himself. Moreover, when experiments are performed with cocaine on animals, and particularly on the monkey, such as Prof. Grasset and Dr. Henri Negre have made, there appear con-

vulsive phenomena characterized by attacks of clonic spasm, and this happens when the dose is reached of six cubic centimetres of a two per cent. solution.

Moreover, cocaine has an evident action on the temperature, which it raises; it is, therefore, a hyperthermic agent. This action, however, is very variable, according to the kind of animal experimented on; for, while cocaine raises the temperature in the dog, it lowers it in the monkey. In fine, my pupil Dr. Rigolet has noted *de visu* the modifications effected in the capillary system by the action of the cocaine. Several drops of a one per cent. solution determine in the frog, at first a dilatation, then a contraction of the capillaries; and Rigolet considers this alkaloid a powerful vaso-constrictor. These experiments give us a physiological explanation of the general symptoms which in man are determined by cocaine.

However, thus far these accidents of a toxic kind have never presented any gravity, and to determine such constitutional effects it is necessary to employ pretty large doses. Thus, Rigolet has been able to inject, without any harm, 40 centigrammes in the veins of a dog weighing 18 kilogrammes. Likewise, Bignon of Lima, has observed that the Indians can absorb as much as 40 centigrammes of cocaine in chewing the leaves, without experiencing any toxic manifestations.

Ordinarily, to obtain the anæsthetic effects, we make use of a two per cent. solution of chlorhydrate

of cocaine. According to the researches which I have made, the increase of the anæsthesia is not proportioned to the increase of dose, so that we may adhere to this two per cent. solution with the certainty of experiencing the desired results.

In certain cases we may employ pomades of cocaine, and in the preparation of these it is not necessary to transform the cocaine into a hydrochlorate. Bignon of Lima has, in fact, shown us that the alkaloids of coca are soluble in unctuous substances of mineral origin, such as vaselin; the dose here is the same as in the case of the solutions; finally, one can have recourse to preparations made from the plant itself. Delpech, in particular, has made an extract of coca according to the method of the American Pharmacopœia—that is, by evaporating the alcohol, and which is said to render good service in affections of the pharynx.

Before undertaking the consideration of the action of coca and its therapeutic applications, I desire to say a few words about its cost.

When Koller's discovery was first made known, cocaine readily brought a very high price, and this was the first drawback to its general use. I have, in fact, known physicians, ignorant of this high cost, to prescribe gargles, lavements, and ointments, the price of which exceeded twenty dollars. To-day cocaine is sold at a much cheaper rate, and you can find in our drug stores cocaine of impure quality, though still

pure enough for all anæsthetic purposes, save in ophthalmic surgery, the price of which varies from four to six francs a gramme.

THERAPEUTIC APPLICATIONS OF COCAINE.

Cocaine is, as we have seen, a local anæsthetic of the mucous membrane and the skin. To begin with the subject of the production of cutaneous anæsthesia, it is necessary, in order that the cocaine may act, that it be applied to an abraded surface, or introduced under the skin. I have never obtained the least effect from the prolonged contact of cocaine with the undenuded skin, whether the alkaloid were rubbed over the derm in the form of concentrated solutions, or in the form of ointment.

When the skin is deprived of its cuticle, and cocaine is applied, the latter has a very marked anæsthetic action, and you can derive advantage from this property in the treatment of *burns*, where solutions or pomades of this alkaloid at once dissipate the pain which accompanies the first and second degrees. You will obtain the same analgesic effects in the case of cracked nipples, so common in nursing women, and Audhoui has reported interesting instances of this kind. In certain pruriginous affections of the skin, moreover, cocaine may be used to allay the tormenting itching.

Administered under the skin, two-per-cent. solutions of cocaine enable us to perform, without pain a great number of minor operations. It is with the

help of this local anæsthetic that I now practice pleurotomy, and that I secure for the patient exemption from the pain of the first stage of the operation. To attain this result, I inject at both extremities of the line which my bistoury has to traverse a syringeful of a two-per-cent. solution of hydrochlorate of cocaine.

You may in this way, without pain, open a superficial abscess, or extirpate a lupus; the pain of incising a felon is much mitigated; by the help of cocaine, tracheotomy is robbed of half its terrors; and, in short, you will derive advantage from the local use of this alkaloid in all instances where the incision of the skin is the chief element of pain. In all these cases the local anæsthesia by cocaine is far superior to that produced by cold. Remember that you should always operate with the patient in a recumbent posture, to avoid the vertigo which might ensue, and you should wait ten minutes, at least, after the subcutaneous injection, before proceeding to the incision of the skin.

By the aid of cocaine I have operated for phymosis, but if you are not very careful you will have difficulty in approximating the skin and mucous membrane with your *serre-fines*, by reason of the artificial œdema produced by the injection of the cocaine solution in the cellular tissue of the prepuce.

I come now to the application of cocaine to the affections of mucous membranes. I shall omit what pertains to the ocular mucosa, this being the special

province of the ophthalmologist, and I shall consider rapidly the benefits derivable from cocaine in affections of the mucous membranes, commencing with the digestive tube.

The buccal and pharyngeal mucous membranes are readily and rapidly anæsthetized by cocaine. In operations on the pharynx, epiglottis, and larynx, generally so painful, you may make applications of this alkaloid, and you have often seen in my service tuberculous patients who could scarcely swallow a mouthful, enabled henceforth to eat by reason of relief from suffering obtained by the repeated use of solutions of this charming local analgesic. You all doubtless remember the case of the late General Grant, and the comfort he obtained the last few months of his life from cocaine.

In the cases of which I have just spoken, the throat is painted with a strong solution of cocaine a few minutes before a meal, and the local anæsthesia lasts about three-quarters of an hour, giving ample time for the repast.

By means of these local applications of cocaine such operations as staphylorraphy are facilitated, and laryngoscopic examinations are rendered comparatively easy; it is also a good plan, in order to avoid the pain of amygdalotomy, either to inject a little cocaine into the tonsil, or, as Lermoyez advises,* to

* Lermoyez, Anæsthesia by Cocaine in Amygdalotomy, Bull. de Thér., t. cviii, p. 108.

paint the tonsils over several times with a two-per-cent. solution before resorting to the operation. Moreover, the painful period in the performance of lavage or gavage of the stomach, due to the contractions which take place in the isthmus of the fauces, may be obviated by painting with cocaine, and I have been careful to resort to this method whenever patients have experienced difficulty in the introduction of the stomach tube.

But the anæsthetic action, so local and superficial, of cocaine, can be of no benefit in toothache or in the extraction of teeth; on this point all the best dental surgeons, such as Galeppe and Magitot, are agreed.

Certain diseases of the œsophagus, such as spasmodic stricture, are tributary to the action of cocaine, which may be applied by means of the sound or by causing solutions to be swallowed.

As for the disorders of the stomach, such as spasmodic affections of this organ with incoercible vomiting, cocaine may sometimes render marked service. Certain perversions of the stomach, and especially bullimia, are also amenable to cocaine, as Beugnier-Corbeau has shown. It is even certain than were cocaine to be bought at a reasonably low price, so that it could be afforded, one might use it to advantage in treating the agonizing pains which attend ulcer and cancer of the stomach, and this might be done by bringing solutions of cocaine directly into contact with the lining membrane of that viscus by means of the syphon tube.

The great benefit which we have derived from the anæsthetizing properties of cocaine in painful affections of the upper part of the digestive tube, has furnished us with indications for its use in certain anal affections. Obissier was one of the first to make application of this remedy in cases of anal fissure.* Before effecting dilatation of the sphincter, he procured complete local anæsthesia by making at two opposite points, just at the margin of the orifice, interstitial injections of two-thirds of a grain of cocaine.

You have seen me have recourse, and successfully, to the same means, aud I have been able in the case of one of our patients affected with fissure of the anus, to perform forcible dilatation without pain. These injections must be made around the sphincter, and I used in the case at which you were present, four injections of a syringeful of a four per cent. solution. Lotions do not suffice, as the unsuccessful trials or Dr. Clemente Ferreira testify.†

You can also have recourse to cocaine in cases of painful hæmorrhoids, and you may here employ suppositories containing one-third of a grain. So much for the mucous membrane of the digestive tube; we will now pass on to that of the genito-urinary organs.

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*Obissier: Note on the employment of Cocaine in Fissnre of Anus, Bull. de Thér., t. cviii. p. 10.

†Clemente Ferreria: A case of fissure of the anus treated without success by hydrochlorate of cocaine, Bull. de Thér., t. cix. p. 216.

It was in this hospital that one of the first applications of cocaine to the treatment of vaginismus was made. It concerned a patient in the service of our colleague Anger, and who had not been benefited by forced dilatation under chloroform. A few swabbings with a solution of cocaine, made by my *interné* Lejars, rendered examination easy, and removed all pain and spasm, and thereafter made sexual approaches possible, as the husband of this woman testified some weeks afterward.*

Almost at the same time Cazin reported to the Society of Surgery a similar case, and since then facts have so multiplied that we may now say that if cocaine does not cure vaginismus, it at any rate greatly alleviates this painful affection in rendering sexual relations possible by the help of inunctions or lotions of this alkaloid.

Gynæcology has even gone further, and by subcutaneous injections and swabbings of the neck of the womb, Doleris has maintained that we may to a certain extent mitigate the pains of childbirth.

The urethral mucous membrane is also advantageously modified by the salts of cocaine. I have derived great benefit therefrom in practicing cauterization of those painful vegetations which form around the meatus urinarius in females. Guyon has em-

* Dujardin-Beaumets: A case of vaginismus treated with success by hydrochlorate of cocaine, Bull. de Thér., t. cvii. p. 489.

ployed cocaine with good effect in the male, to relieve the pain and spasm accompanying catheterism.

Finally, the respiratory and nasal mucous membranes have also derived advantage from this anæsthetic action, when it has been a case of the extraction of polypi from the nose or the application of caustic solutions to the larynx, At the same time it is necessary to bear in mind the paralyzing action of cocaine; and in a case described by Ayssaguier, grave asphyxiating phenomena were seen to follow painting the larynx with this alkaloid. In fine, to complete the subject, I must tell you that otologists have also utilized cocaine in the treatment of affections of the ear.

To sum up, whenever you desire to obtain an anæsthesia of the skin and mucous membranes which shall be complete, temporary, and of little extent, you may utilize cocaine. Are there other substances capable of producing local anæsthesĭa of the tissues? This is a question which the future alone can decide. For my part I have tried caffeine, and if it diminshes the sensibility of the conjunctivia, it does this very imperfectly. It has been claimed that menthol has the same effect, but the trials which I have made with this substance have not given me any satisfactory results. Cocaine remains, then, thus far the only local anæsthetic of the mucous membranes, and this fact renders the introduction of this alkaloid into medicine one of the most precious therapeutic acquisitions of the age.

Since I have spoken to you of hypnotics, allow me finish this lecture by announcing the discovery by Dr. Bardet and myself of a powerful hypnotic.

Among the different products of the great aromatic series which we are studying at the present time in their chemical constitution and therapeutic action, is found a mixed aceton having for formula C_6, H_6, CO, CH_3; it is *phenyl-methyl aceton*, or *acetophenon*. This body had been already studied by Popof and Nencki, who observed that this aceton is transformed in the economy into carbonic and benzoic acids, and eliminated by the urine in the state of hippurates.

We have found in this aceton remarkable hypnotic properties; hence we propose to substitute for its compound name the shorter appellation of *hypnon*.

Administered to the adult in the dose of from two to four drops, hypnon causes sleep, and in the insomnia determined by alcoholism its effects seem superior to those of chloral and paraldehyd.

When you inject under the skin of Guinea-pigs fifty centigrammes to a gramme of hypnon in a state of purity, you determine insensibility, then a comatose state, in which the animal succumbs in the course of five to six hours. Hypnon is, as you see, a body which is liquid at the ordinary temperature, having a very strong odor which resembles that of cherry-laurel and new-mown hay; it is not soluble in water, and therefore we have given it dissolved in glycerin inclosed in capsules.

Our patients have not experienced any unpleasant effects from it, save always the disagreeable odor of the breath which results from its elimination by the lungs.

What future is in reserve for this hypnotic we do not fully know, but I thought it worth the while, in concluding, to allude to this discovery which results from researches in which most of you have participated.

[To the readers of this work, the Translator would commend as supplementary to it, the series of articles by the same author, entitled "New Therapeutic Agencies," published in the Therapeutic Gazette, 1889–90.]

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